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ANNUAL REPORT
OF
PROGRAM ACTIVITIES
NATIONAL CANCER INSTITUTE
Fiscal Year 1981
Part II-A

U. S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service National Institutes of Health

ANNUAL REPORT

OF

PROGRAM ACTIVITIES

NATIONAL CANCER INSTITUTE

Fiscal Year 1981

Part II-A

Division of Cancer Biology and Diagnosis

DIVISION OF CANCER BIOLOGY AND DIAGNOSIS

ANNUAL REPORT

October 1, 1980 through September 30, 1981

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EXTRAMURAL RESEARCH PROGRAM

DIVISION OF CANCER BIOLOGY AND DIAGNOSIS

The Extramural Research Program covers four broad scientific areas: Tumor Biology, Immunology, Cancer Diagnosis and Breast Cancer Program. The first two are primarily grant based efforts, the latter programs employ both contracts and grants in supporting the sceintists at large.

Three years ago, an effort was started to convert then primarily contract based program to one oriented on R01 and P01 grants. In this year we witness a successful achievement of this goal. With exception of the Cancer Diagnosis Program, where clinical evaluations and instrument developments will continue to be supported by contracts, the remaining programs will concentrate almost exclusively on grants.

Another change in the management of the DCBD Extramural Research Program concerns the Advisory Committees, which have slowly been deactivated during the past year. At the end of this year only the Breast Cancer Task Force will continue as an active body advising the staff of this organ site program. On the other hand, the Board of Scientific Counselors will enlarge its responsibilities to cover the entire division. It will review the program annually, provide concept review on new projects and act as site visit team to intramural laboratories and branches. Senior staff review for relevance will be carried out as before by the Steering Committee consisting of NCI personnel.

The extramural research budget this year reached $138,000,000 of which $126,000,000 were in grant supported projects and $12,000,000 in contracts (including this Division's share of the FCRC effort).

The Tumor Biology Program supports a broad spectrum of basic biological and biochemical research in the pursuit of one goal, defining properties of cancer cells and tumors that uniquely distinguish them from normal, healthy cells and tissues. If we could define these properties and learn how to manipulate the biological signals or modify biochemical reactions responsible for the aberrant behavior of cancer cells, applied methods could be developed for the successful diagnosis and therapy of cancer patients. The three areas of investigation which correspond to different theories of how to control the development and progression of neoplastic disease include understanding the basic biochemical mechanisms involved in growth control, studies of the changes that occur at the molecular level which lead to cancer cell invasion and accession of detailed biological and biochemical information about the processes which induce cancer cell differentiation. If the genetic program of an actively growing cancer could be changed to one of terminal differentiation, then the malignant tumor could be rendered harmless. The above emphasis of the Tumor Biology Program in the areas of growth, invasion and differentiation provides a convenient and purposeful way of viewing the role of basic biological research with the ultimate goal of curing cancer.

The scope of the Tumor Biology Program has changed considerably over the last five years. Mostly, this has been due to research advances in our knowledge of

gene expression and growth requirements of eukaryotic cells, as well as technical advancements in somatic cell genetics, somatic cell hybridization and DNA recombinant biology. The Tumor Biology Program has become increasingly focused on the properties of cancer cells rather than on the cell biology of eukaryotic cells.

Immunology Program of the National Cancer Institute supports studies which contribute to an understanding of the role of the immune system on the development, growth and spread of tumors. In line with organizational changes within the Institute, the emphasis for the Immunology Program is now centered upon mechanistic studies with responsibility for the more applied immunological efforts in detection and diagnosis residing in the Diagnosis Program and responsibility for explicit treatment studies involving immunologic manipulation residing in the programs of the Division of Cancer Treatment.

Some of the more obvious areas supported by the Immunology Program include studies in: molecular genetics and biology of immunoglobulins, natural cell mediated immunity, monoclonal antibodies and immune response genes. Following conferences and meetings were supported by the Program: "Mechanisms in Human Cancer Immunology Symposion", "Host Defense in Neoplasia" and "Mechanisms in Cell Mediated Cytoxicity". To illustrate the program more specifically, the following activities were supported: the synthesis, structure and mechanism of action of antibodies capable of reacting with tumor cells and of humoral factors other than antibody which participate, activate and regulate the immune response to tumors: complement, interferon, lymphokines, lymphoid cell growth factors, helper factors and suppressor factors. Other studies covered were the immunobiology of lymphocytes, monocytes and macrophages that participate in anti-tumor responses including their development, heterogeneity, interactions and mechanisms of action.

Considerable effort was devoted to the identification,isolation and characterization of cell surface determinants which serve as target antigens for the immune response to tumors and of cell surface determinants of lymphocytes and macrophages which are involved in actual responses of these cells to tumors. Immune surveillance against the development of tumors of various origins by all immune mechanisms included studies on T cell immunity, macrophage reactivity, natural killer cell activity, etc.

The Cancer Diagnosis Research Program emphasizes research in early detection, diagnosis, tumor localization, and monitoring of the disease. The major objective of the Program is to recognize or detect cancer at the earliest possible stage to allow appropriate therapy which should improve the chances for the control of cancer.

The Diagnosis Research Program consists of projects in eight disciplinary categories: biochemistry, immunodiagnosis, cytology, pathology, radiological imaging, non-radiological imaging, nuclear medicine and multiple disciplinary projects. Biomedical methods of diagnosis and detection involve a variety of substances such as hormones, enzymes, proteins and metabolic products, surface characteristics of tumor cells and their chemical characterization. Immunodiagnosis projects can be subdivided into those dealing with circulating tumor antigens or markers, such as oncofetal antigens, hormones, enzymes, and glycoproteins; projects dealing with tumor associated antigens, studies of lymphocytes and projects dealing with antibodies to tumors.

Diagnostic cytology research projects include the development and testing instrumentation and cell markers that can be used to differentiate normal and atypical cells. Imaging studies in this program use conventional x-ray approach with the goal of reducing the exposure doses without compromising the quality of imgages. Another arm involves methods other than x-ray and radionuclides; such as the use of proton and heavy ion beams, nuclear magnetic resonance (NMR), ultrasound, and thermography. Finally, Diagnosis Program supports the research on screening of lung, colon and endometrial cancers.

Breast Cancer Program promotes and supports multidisciplinary research projects that will lead to improved methods of diagnosis, prognosis, treatment and prevention of breast cancer. This is the oldest organ site program and the only one managed by NCI personnel exclusively. To help direct the program, advise from the Breast Cancer Task Force Committee is obtained, whose members suggest areas in need of emphasis, innovative research ideas and workshop topics aimed at exploring rapidly developing areas. The following topics exemplify the field coverage: "Luteal Phase Defects and Breast Cancer Risk", "Clonogenic Assays and Chemotherapy Sensitivity", "Chemical Carcinogen-Hormone Interaction in Transformation of Mammary Epithelial Cells In Vitro", "Monoclonal Antibodies in Breast Cancer", and "Diet and Breast Cancer Risk".

The staff of the Branch organizes requests for investigator-initiated applications (RFA's) or Program Announcements (PA's), and requests for contract proposals (RFP's) depending upon the mechanism of funding considered. In addition, there exists an information section responsible for monthly production of the publication Intercom which provides up-to-date listings of scientific papers on breast cancer research in biology, epidemiology, diagnosis, and treatment; a list of meetings and conferences related to the disease; and abstracts of presentations made at workshops. The publication is sent to investigators and institutions throughout the world. Another publication of the Intracom provides abstracts or summaries of the published literature as well as those on grant and contract activites.

TUMOR BIOLOGY PROGRAM

Description

The Tumor Biology Program supports a broad spectrum of basic biological and biochemical research (See Appendix I) in the pursuit of one overriding goal, defining properties of cancer cells and tumors that uniquely distinguish them from normal, healthy cells and tissues. The supposition is that if we can define these properties and learn how to manipulate or change the biological signals and/or modify biochemical reactions responsible for the aberrant behavior of cancer cells, applied methods can be developed for the successful treatment, diagnosis and therapy of cancer patients. Within this goal are three major areas of investigation which correspond to different theories of how to control the development and progression of neoplastic disease. The first is understanding the basic biochemical mechanisms involved in growth control, whether these involve particular external signals that initiate the process of cell division or particular internal molecules more directly responsible for DNA replication and metabolism. This kind of information can lead to the development of specific hormonal and drug therapies. The second is studying changes that occur at the molecular level which lead to cancer cell invasion. The invasive behavior of cancer cells is a prerequisite to malignancy, or the ability of tumors to invade surrounding tissues, escape normal host defense mechanisms and become established at multiple secondary metastatic sites. Theoretically, if the invasive properties of malignant tumors can be controlled and these tumors confined to particular sites, metastasis, the major killer in cancer patients, will not occur. The third is to develop detailed biological and biochemical information about the processes which induce cancer cell differentiation. There is good reason to believe that many kinds of cancers will respond to external stimuli and differentiate. If the genetic program of an actively growing cancer could be changed to one of terminal differentiation, then the malignant tumor could be rendered harmless. Although the above emphasis of the Tumor Biology Program in the areas of growth, invasion and differentiation is stated in simple terms, it provides a convenient and purposeful way of viewing the role of basic biological research to the ultimate goal of curing cancer.

The kinds of information developed in the Tumor Biology Program provide a foundation for and relate directly or indirectly to nearly every other program area within the National Cancer Institute. The importance of basic tumor biology research to the National Cancer Plan is reflected by the large $50 million commitment of the NCI to this program area in FY 1981 (See Table I). Appendix II provides a complete listing of all grants supported by the Tumor Biology Program.

Selected Scientific Developments

A. Tumor Cell Invasiveness:

The most lethal property of malignant cells is their ability to metastasize to distant sites. However, before metastases can be established, the malignant cell must invade the surrounding tissues. Because an understanding of the invasive process remains a central problem for tumor biology, the Tumor Biology Program organized and sponsored a "Tumor Cell Invasion Workshop." Three areas were chosen for discussion: (1) Methods and Models for Studying Tumor Cell Invasion; (2) Tumor Cell Penetration of the Extracellular Matrix; and (3) The Role of Cell Motility in the Invasive Process. The objectives of the workshop were to bring a small group of scientists together for a day and a half to explore the state-of-the-art in these three areas and, through an emphasis on discussion rather than formal presentation, to define the limitations of current experimental approaches and to suggest new approaches required to advance our knowledge of the field. The participants were carefully chosen from both the U.S. and foreign countries for their current research interest in problems related to invasive and metastatic processes and for their diversity of training from biochemistry to embryology to pathology. This was a unique group of individuals (See Appendix III).

Several major issues were brought to the group's attention before any substantive discussion of the three major topics was initiated. First, there was a recognized problem between the basic scientists and the pathologists in the use of the term malignant. It was generally agreed that it is not appropriate to use *in vitro* criteria alone to call a tumor cell malignant; thus, viral transformation or any other kind of transformation should not be referred to as malignant transformation unless this could be confirmed by accepted *in vivo* criteria. No one could agree upon whether malignant should refer to a tumor that kills or a tumor that metastasizes or a tumor that invades the surrounding tissue or all three. Unfortunately, some kinds of tumors (e.g. basal cell carcinomas and primary tumors of the brain) kill the patient but do not invade or metastasize. There is no doubt that an acceptable definition is required for malignancy that satisfies both clinical situations and experimental systems if contradictions and confusions in the scientific literature are to be avoided in the future. Furthermore, invasion is currently defined very crudely by what a pathologist sees in a microscope. Everyone agreed that a rigorous definition of invasion is not possible until the invasive process can be measured (i.e. there are clear measurable markers). The second issue discussed was more a reminder to the group that invasiveness is not a unique property of tumor cells. During embryonic development, many different kinds of cells show periods of invasive behavior; in post-natal life, melanocytes, capillary endothelial cells and several classes of white blood cells retain their invasive properties. This is an important point because tumors have never been shown to exhibit any behavior or property that is completely tumor-specific. This is a basic reason why the cancerous

process is so difficult to deal with both experimentally and clinically. The third issue which captured the entire groups attention and which offered the greatest challenges and implications for experimental analysis of the invasive phenotype, was phenotypic heterogenity of cell populations within a tumor. George Poste (CA 30192) presented startling information that cloned B16 mouse melanoma cell lines, selected for their increased metastatic potential or low metastatic potential, formed tumors that were very unstable; the population of cells within a tumor apparently derived from a single clone, generated phenotype heterogeneity with respect to invasive properties or drug sensitivity very quickly. Subsequent to Poste's presentation, this observation was surprisingly confirmed by Fidler using a different cloned melanoma system, by Heppner (CA 27419) using a variety of cloned mouse mammary tumor cell lines and by Varani (CA 29550) using cloned mouse fibrosarcoma cells. It was postulated that the stability of any given tumor cell phenotype depended upon the interaction or presence of other phenotypes; clearly, one cloned tumor phenotype is not likely to persist in an in vivo situation. Thus, the problem of heterogeneity has very serious implications that must be dealt with experimentally if we are to learn more about the invasive phenotype.

Ideally, model systems for studying the invasive process should be (1) amenable to a combination of in vitro and in vivo techniques; (2) permit quantitation of invasion and; (3) allow for recovery of invasive cells for further study. There are no model systems that fulfill all these criteria, but there are a number of useful approaches for studying invasion that have been developed within the last few years. Poste (CA 30192) has developed a system whereby tumor cells are measured for their ability to penetrate various natural membranes and/or membrane-cell-matrix structures; this technique offers great promise because the matrix that is invaded can be varied and cells recovered on the basis of their relative invasive properties. Peter Jones presented a culture system in which smooth muscle cells are layered on a tissue culture dish followed by endothelial cells; a clear basal lamina forms between these two kinds of cells, which closely resembles the in vivo situation. When human fibrosarcoma cells were layered on this cell matrix, they penetrated readily and this penetration was accompanied by proteolytic activity. This model allows for quantitation of release of tissue proteins as well as histological correlates of the invasive process. Pauli's system (Pauli et al., 1980) used carcinogen induced bladder carcinomas and had the advantage that it correlated in vitro and in vivo studies well. X-ray analysis in vivo could demonstrate invasion into baby rat bone; cell lines in vitro derived from the same bladder carcinoma could be studied for their invasion of cartilage. Reich presented a very interesting system for measuring invasion; human cancer cells were layered on the allantoic membrane of a fertilized chicken egg. The lungs of the chicken embryo were measured for human plasminogen activator as the measure of invasion. There were other model systems briefly discussed but these were not new to the field. All model systems require an appropriate cell as well as an appropriate stroma that is to be invaded. Although significant progress has been made in developing new model systems, a major problem is that the cells used have not had their biological properties adequately defined. This is especially important to consider if we are to assume that phenotypic heterogeneity rather than stability is the more likely situation encountered in vivo.

Penetration of the extracellular matrix by tumor cells is fundamental to our understanding of the invasive proocess. This section of the workshop was perhaps the most interesting in terms of new information provided. The most striking information was provided by Kuettner (CA 21566) in his description of recent information about the complex structure of the extracellular matrix. While only a few years ago, the extracellular matrix was believed to consist primarily of collagen, now it has been established that there are many different genotypic collagens, tissue-specific proteoglycans, laminin and fibronection. The latter two components have been the subject of intense investigations because of their apparent involvement in cell-cell interactions. Furthermore, the matrix is highly underhydrated, which would lead one to believe that molecules such as nutrients and proteins might have considerable difficulty passing through the matrix. However, Pietro Gullino presented information that the matrix (i.e. interstitial space) does exchange fluids, nutrients and proteins very rapidly with the vascular system; thus, the matrix is a very dynamic structure. Many of the participants demonstrated that there are specific degradative enzymes for each component within the matrix, and there was good reason to believe that each degradative enzyme could be inhibited by a specific inhibitor. This explains why past research efforts to correlate one kind of collagenase activity with tumor cell invasiveness have been unsuccessful. There are many enzymatic activities and inhibitory activities to consider. Furthermore, the development of tumor heterogeneity can create microenvironments which stimulate the production of key enzymes and/or inhibitors that initiate the invasive process. Although the participants in the workshop favored the hypothesis that the degradative activity of enzymes produced by the tumor or the host are actively involved in the invasive process, they could not rule out a simpler physical process. However, all of the discussion pointed toward a very active system in which the environment could trigger many different enzymatic or inhibitory activities. Everyone agreed that further research should carefully define the nature of the matrix being studied and the specificity of the enzyme being studied, as well as determine whether natural inhibitors of the enzyme were present under different conditions.

The motility of the tumor cell is essential if it is to move from the primary tumor and reach the vascular and lymphatic systems. Because there has been a considerable emphasis in the literature which describes the fibriullar networks within tumor cells that may be responsible for cell motility, this area was not discussed thoroughly. No compelling evidence was presented to support the hypothesis that tumor cells are intrinsically more motile than their corresponding normal cells. Ward (Orr et al., 1979); Wass et al., 1980) discussed the possibility that tumor cells respond to chemotactic factors, supporting the possibility that tumor cell invasion is an active, directional process. He believed that his information supported a model in which tumor cells moved similarly to leukocytes in response to factors. This is an interesting theory because tumor cell exodus from the primary site has often been observed to follow leukocytes through the same channels. Furthermore, capillary growth toward tumors, as discussed in the next section, may follow the path of infiltrating leukocytes. There could be some interesting common denominators relating tumor cell invasion, capillary invasion, and leukocyte motility.

Varani (CA 29950), using mouse fibrosarcoma cells, showed data which supported non-directed motility as another component of tumor cell migration. By altering the surface components responsible for cell adhesion, a clear correlation could be made between decreased cell motility, increased cell adhesion in vitro and tumor takes after sub-cutaneous injection in vivo.

To summarize, better model systems are critical to experimental analysis of the invasive process. Invasion of tissue matrices by both normal and tumor cells appears to involve a combination of tissue destruction (i.e. degradative enzymes and inhibitors of degradative enzymes) and directional movement (i.e. chemotactic factors). The microenvironment of the host and tumor heterogeneity are likely to be critical factors in understanding what controls the invasive process.

B. Angiogenesis

The importance of tumor vascularization to tumor growth has been recognized for many years. Most solid malignant tumors have the capacity to induce the generation of new capillary growth to meet their ever increasing requirement of blood supply. The phenomenon, called angiogenesis, is a topic of great interest to the Tumor Biology Program. Certain recent developments from the projects supported through the program have encouraged the suggestion that control of tumor growth through therapy with antiangiogenetic factors may be possible. Three processes appear to contribute to the overall process of capillary growth: 1) degradation of basement membrane of the blood vessel in the area of a developing outgrowth; 2) endothelial cell migration and; 3) endothelial cell replication. Sophisticated systems have been designed to investigate each of these processes.

Folkman et al.(1971), first described a Tumor Angiogenesis Factor (TAF) that promoted the invasion of an avascular area by capillaries. Production of sufficient quantities of the factor (or factors) to allow purification and characterization has, however, been an extremely difficult problem. For years only complicated in vivo assays were available to test for the factor and the results were only semi-quantitative.

In 1976, Fenselau and Mello described an in vitro assay for TAF. Homogenates of Walker 256 carcinoma stimulated proliferation of endothelial cells prepared from fetal bovine aorta. A big breakthrough came in 1979 when Folkman and associates reported development of a cloned long-term culture of bovine capillary endothelial cells, the growth of which required the presence of media pre-conditioned by incubation with cells from sarcoma 180 tumors. The tumor-derived angiogenesis factors not only induced proliferation of the capillary endothelial cells but migration as well. This migration could be quantitated and was proportional to the concentration of tumor-conditioned medium present (Zetter,1980). These in vitro systems, then, seem to support what has been observed in vivo, that neovascularization involves the migration of endothelial cells from pre-existing vessels towards the source of the angiogenesis factor and that there is a directional elongation of growth of new capillary sprouts. These same cloned endothelial cells under the proper culture conditions, with the tumor-derived factors, will organize into capillary tubes, form branches and assemble an entire capillary network. This appears to be the first demonstration of in vitro angiogenesis (Folkman and Haudenschild, 1980).

Although attempts to characterize TAF have still not provided definitive information about molecular structure, Fenselau et al. (1981) now report the preparation of purified material from the Walker 256 rat tumor with a molecular weight of less than 800 daltons. The factor is mitogenic for endothelial cells and induces neovascularization in an *in vivo* assay.

Another recent report (Azizkhan et al., 1980), indicates that a product of mast cells (a type of white blood cell), probably heparin, also stimulates the migration of the cultured bovine capillary endothelial cells without inducing proliferation. Since the accumulation of mast cells at a tumor site precedes the arrival of new blood vessels, the mast cell product may somehow direct the construction of the new vasculature.

The third process of neovascularization, the fragmentation of the existing basement membrane of the blood vessel at the point of new capillary growth, and the ability of these new sprouts to invade surrounding tissues, suggests the activation of proteolytic activity. Rifkin and associates (Moscatelli et al., 1980) have been able to demonstrate the production of collagenase from cultured human endothelial cells by stimulation with the tumor promoter 12-0-tetradecanoyl phorbol-13-acetate. Thus, one more response to angiogenic stimuli may be the increased secretion of collagenase.

Although little is known about the factors that contribute to angiogenesis, it has been possible to inhibit their activity. Unfortunately, the inhibitory factors have been as elusive as the stimulatory factors. One approach has been the preparation of specific protease and collagenase inhibitors that prevent vascular invasion. These are found in a variety of cell types. Another has focused on extraction products of cartilage, a unique tissue in that it normally is devoid of any vasculature. The natural resistance of cartilage to tumor invasion has been well documented (Kuettner and Pauli, 1981) and also appears to be due in part to endogenous protease inhibitors. In *in vivo* assay systems, invading capillaries moving towards a tumor stimulus grow around but cannot invade implanted pieces of cartilage. Extracts of cartilage inhibited vascular growth when infused into live animals bearing tumor implants in their eyes (Langer et al., 1980). The extract had no effect on cultured cells of the same tumor type. In the culture system of capillary endothelial cells, migration induced by tumor-derived factors is also inhibited by the presence of leukocyte interferon (Brouty-Boye and Zetter, 1980).

Prevention of angiogenesis could have an extraordinary effect on cancer treatment. The inhibitors so far identified are all natural products so that side effects are minimal. Furthermore, the effects seem to be specific for endothelial cells--they prevent new vascularization only. The next few years should produce some exciting new developments.

C. Teratocarcinoma

Some intriguing and potentially useful new developments in research with the teratocarcinoma cell system also warrant special attention in this report. Tumors, derived from germ cells, which develop in the ovary or testis of mice and humans, may be of either of two types. Teratocarcinomas are malignant

tumors which grow from embryonal carcinoma cells themselves derived from germ cells. These embryonal carcinoma cells are "stem" cells which may continue to proliferate or may differentiate into chaotic arrangements of somatic cells typical to an embryo. If all the cells differentiate the tumors become benign and are known as teratomas. Embryonal carcinoma cells from the teratocarcinomas have been established in vitro and provide the special model system now used extensively in research. Certain of the cell lines (PSA-1, for example) retain their totipotent character and will produce a variety of differentiated cell types in vitro or in vivo, while some variants (F9, for example) have become nullipotent and will not differentiate spontaneously, but simply keep replicating.

The development of transplantable teratocarcinomas in mice can be attributed to the work of Leroy Stevens (1980). He has defined both genetic and environmental factors involved in the tumorigenesis and supplied the transplantable teratocarcinomas to the rest of the research community. However, it was Pierce and co-workers (1967) who first formulated a theory, prompted by this cell system, that differentiation of stem cells within a tumor might deplete the malignant element and result in a benign neoplasm. The implication of this was a new approach to cancer therapy.

The demonstration (Mintz et al., 1975), that microinjection of mouse teratocarcinoma cells into blastocysts from normal mice and subsequent implantation into the uteri of pseudopregnant females resulted in the formation of normal chimeric mice, was noteworthy for its suggestion that malignancy was not the result of a special gene content but rather of the regulation of genes. The mechanism whereby the 80-cell-blastocyst can shut down the "malignancy" of embryonal carcinoma cells is unknown, however, there is a limit to the number of carcinoma cells they can tolerate. Injection of 20 malignant cells into a normal blastocyst results in the birth of chimeric offspring bearing tumors (Papaioannou, 1975). In fact, it was recently shown (Pierce et al., 1979) that control of malignancy is lost when the blastocyst contains more then two embryonal carcinoma cells. When three or more cells are injected into the blastocyst the hybrid cell mass forms tumors typical of embryonal carinoma in the peritoneum of mice.

One of the best studied teratocarcinoma cell lines, the F9, does not undergo spontaneous differentiation although it can be induced to differentiate by treatment with retinoic acid and other compounds. Further the F9 cells, when infected with SV40 virus do not support replication of the virus nor express the typical virus-specific antigens. After retinoic acid induction of the cells, the antigens are expressed. Analagous results have been attained with a more sophisticated F9 clone transformed with a plasmid containing SV40 genes linked to a herpes simplex virus thymidine kinase. The cell line expresses the thymidine kinase but does not express the adjacent viral antigens unless treated with retinoic acid (Linnenback et al., 1980)

The majority of teratocarcinoma cell culture systems maintain their pluripotency and become benign differentiated cell types in vitro, with limited lifespans. However when cultures are initiated with a 1:1 mixture of pluripotent (PSA-1) and nullipotent (the F9) cells, the environment restricts differentiation of the

PSA-1 cells and they begin to die. No detectable inhibitor from the F9 cells has yet been found (Rosenstraus and Levine, 1979). Hybrid cells prepared by fusion of pluripotent with nullipotent teratocarcinoma cells have been studied independently by two different groups to determine which characteristic is dominant. Rosenstraus et al (1980) reported that such hybrids, when injected into mice, developed tumors with the characteristics of the pluripotent cells, i.e., they had a spectrum of differentiated tissue. Oshima et al (1981), in contrast, prepared similar hybrids and observed the growth of tumors that were 95 - 100% embryonal carcinoma stem cells.

Another related research project which exploits the teratocarcinoma system is that of Martin. She is attempting to explain the inactivation of one of the X chromosomes in the female mouse zygote that occurs at about day four during normal embryological development. Certain of the embryonal carcinoma cell lines from ovarian tumors have two active X chromosomes and during differentiation one of these is inactivated, so the dissection of the related events may be possible (Martin, et al., 1978).

The Tumor Biology Program has begun to formulate an outline for a workshop on teratocarcinoma to be held during the next fiscal year. A survey of selected investigators throughout the country indicates that this would be an ideal time to organize such a conference. Investigators currently in this arena are embryologists, biologists, pathologists and immunologists but molecular biologists and geneticists and biochemists, all with their special techniques, must also be encouraged to get involved, perhaps through collaborations. It is also an important time to delineate both the limitations and the potentials of the teratocarcinoma system. retinoic acid (Linnenback et al., 1980).

D. A Unifying Hypothesis for Neoplastic Transformation

A major frustration of tumor biology has been that each kind of cancer appears to be a different disease. Comparative studies of normal and cancer cells always show rather striking differences, but these differences are never exactly the same for each kind of cancer. An intriguing set of hypotheses has been postulated that may unify many apparently disparate observations of the past and present. During the past decade, protein phosphorylation reactions (protein kinase activity) have been found to function in the regulation of a large number of cellular processes. In fact, a unique class of protein kinases appears to participate in malignant transformation (Langan, 1980). The best studied system is the transformation of cells by Rous sarcoma virus. The transforming protein appears to be a protein kinase (src protein kinase); in addition, cells uninfected by the virus appear to produce a very similar if not identical protein but at a much lower level. Although this observation is interesting in itself, Racker and his colleagues have recently confirmed that the enzyme Na^+/K^+ ATPase which controls the sodium-potassium balance of the cell is not only inefficient in cancer cells but that its activity is controlled by a cascade of different protein kinases. Surprisingly, the src protein kinase and the first kinase in

the cascade of events that activates the Na^+/K^+ ATP'ase crossreact immunologically and are similar by other structural criteria. Thus, this is the first time that a transforming gene product has been linked to the disruption of a specific process in the cell. Racker postulates that these protein kinases may trigger a whole assortment of biochemical changes leading to various neoplastic phenotypes. Even more speculative is that oncogenic viruses originate from movable elements within the genome (i.e. transposons)and have carried away proto-oncogenes (e.g. protein kinases) which are normally present in the cellular DNA (Fox, 1981). Coincidentally, it has been postulated that human cancers arise more frequently from genetic transpositions rather than from conventional mutational events (Cairns, 1981). Proto-oncogenes in the normal genome are not just speculation because several laboratories have now shown that host genes involved in neoplastic transformation can be detected by DNA-mediated gene transfer experiments (Rigby, 1981). Thus, a more unifying hypothesis for neoplastic transformation might include the following:

(1) Many normal cells contain proto-oncogenes.
(2) Transforming viruses not only contain genes derived from host proto-oncogenes but also originate from the movable genetic elements within the cell (i.e. transposons).
(3) Transpositions of proto-oncogenes which allow for increased genetic expression result in the neoplastic phenotype.
(4) Proto-oncogenes are often protein kinases.

Obviously, the above model is highly speculative and many questions remain unanswered and untested, but the very real possibility that there may be some general simplicity attributed to many transformation processes is intriguing and exciting.

E. Tumor Markers

One of the common threads interwoven throughout the literature of cancer biology is a wide-ranging abnormality of gene expression (Weinhouse, 1980). One reason why the early diagnosis of cancer has improved is because different kinds of cancers typically produce enzymes or hormones that are not normally associated with the tissue of origin. Unfortunately, these so-called "tumor markers" have never been identified as specific qualitative differences between a normal and cancer cell, but always seem to represent quantitative differences due to abnormalities of gene regulation that result in a different programming of protein synthesis. Tumor markers may, however, provide important clues about the initiation and progression of malignant disease. Several investigators have documented the presence of altered glycoproteins on the surface of transformed and malignant cells. These have prompted speculation that membrane-bound glycoproteins may mediate the abnormal behavior of cancer cells. These studies also have stimulated a search for soluble glycoprotein tumor markers in biological fluids which are a product of some-kind of "shedding" process. Several years ago a cancer-associated galactosyl transferase isoenzyme was reported. This study has been carried further,

and it has now been established that in the sera of patients with localized neoplasia, there is also a distinctive glycopeptide that functions as an acceptor for the galactosyl transferase isoenzyme. Paradoxically, this glycopeptide inhibits tumor growth in tissue culture and in animal models. However, one speculation is that it represents a host defense product that is produced too late and in insufficient concentrations to effect a clinical remission (Podolsky and Isselbacher, 1980). It is hoped that a further understanding of this glycopeptide's role in affecting the natural growth of malignant cells will not only establish its value as a diagnostic indicator but also as a biological response modifier. Another laboratory has reported the presence of a specific glycoprotein with a molecular weight of 50,000-55,000 which is significantly elevated in the sera from cancer patients with localized or metastatic malignancies (Bolmer and Davidson, 1981). The ectopic production of glycoprotein hormones and their subunits is regularly reported in cancer patients (e.g. Blackman et al, 1980). With the development of better methods of purifying and detecting glycoproteins (e.g. monoclonal antibodies) there is every reason to believe that we will learn a great deal more about the significance of glycoprotein cancer markers in tumorigenesis.

F. Malignancy as a Dominant or Recessive Trait

For the last five years there has been considerable controversy over whether the transformed phenotype in vitro and tumorigenicity in vivo are expressed as recessive or dominant traits in animals cells. To help answer this question somatic cell hybridization techniques have been used in which normal and tumorigenic cells are fused and the resulting hybrids are tested for normal and transformed properties, as well as tumorigenicity. Unfortunately, despite intensive efforts to determine the recessiveness or dominance of malignant traits, the question remains confused. In nearly every case, the expression of cell transformation and tumorigenicity is dominant in viral-transformed cells. But in the case of non-virally transformed cells of either rodent or human origin, the answer is not clear; some results with somatic cell hybrids demonstrate dominance while others suggest recessiveness. The emergence of chromosome-mediated and DNA-mediated gene transfer techniques should be valuable tools to test whether the results obtained by somatic hybridization

are correct. We are now at the stage where it should be possible to clone some of the cancer genes using the DNA mediated transfer approach and recombinant DNA technologies. The availability of cloned mammalian cancer genes should allow a detailed study of their structure and organization and of the regulation of their expression. Furthermore, the possibility of introducing entire cancer chromosomes or cloned cancer genes into pluripotent teratocarcinoma stem cells (see above) should provide valuable insights about their regulation during cell differentiation and development (Croce, 1980).

TABLE I

FISCAL YEAR 1981

TUMOR BIOLOGY PROGRAM

SUMMARY BY SUB-CATEGORY (DOLLARS IN THOUSANDS)

	NON-COMPETING		COMPETING		TOTAL	
	NO.	AMOUNT	NO.	AMOUNT	NO.	AMOUNT
CELL SURFACE	60	$ 5,540	21	$ 1,596	81	$ 7,136
ENZYMES	27	2,493	7	803	34	3,296
PEPTIDE HORMONES	10	848	6	617	16	1,465
STEROIDS	15	1,374	8	581	23	1,955
MEMBRANEOUS ORGANELLES	7	1,488	2	154	9	1,642
RIBOSOMES AND POLYRIBOSOMES	6	892	3	333	9	1,225
M-RNA	10	1,382	7	623	17	2,005
T-RNA	11	1,100	2	250	13	1,350
DNA	11	893	2	341	13	1,234
GROWTH FACTORS	11	1,245	9	1,031	20	2,276
NUCLEUS	13	1,199	6	412	19	1,611
CONTRACTILE ELEMENTS	7	636	3	213	10	849
DEVELOPMENT AND DIFFERENTIATION	40	3,737	19	1,832	59	5,569
CELL GROWTH, CELL DIVISION	30	2,685	7	741	37	3,426
SOMATIC CELL GENETICS	7	859	5	560	12	1,419
INHERITANCE OF NEOPLASMS	0	0	1	51	1	51
PLASMIDS, VIRUSES	6	809	5	342	11	1,151
IN VIVO AND IN VITRO TUMOR LINES	7	633	5	353	12	986
DIFFICULT-TO-CLASSIFY	4	525	1	123	5	648
SUB-TOTAL	282	28,338	119	10,956	401	39,294
PROGRAM PROJECTS	14	7,808	3	2,376	17	10,184
CONFERENCES	1	90	5	99	6	189
YOUNG INVESTIGATORS	14	707	7	333	21	1,040
SUB-TOTAL	29	8,605	15	2,808	44	11,413
TOTAL	311	$36,943	134	$13,764	445	$50,707

APPENDIX I

TUMOR BIOLOGY REFERRAL GUIDELINES

The Tumor Biology Program supports a broad spectrum of research with animal and human cell systems which includes fundamental and comparative studies in histology, pathology, cell biology, developmental biology, molecular biology, embryology, biochemistry, and genetics. The goal of this program is to develop a better understanding of the biological processes in tumors and tumor cells that are responsible for uncontrolled growth and invasion of surrounding tissues. The majority of studies are aimed at determining characteristic differences in structure, function, biochemical composition and molecular mechanisms between normal and neoplastic cells or between progressive states of tumor development and differentiation. Areas supported include:

- Tumor Progression (e.g., angiogenesis, neovascularization, invasiveness, metastasis)
- Differentiation and Neoplasia (e.g., teratomas, teratocarcinomas, hepatomas, neuroblastomas, melanomas, Friend leukemias)
- Genetics of Neoplasia (e.g., karyotypes, somatic cell genetics, somatic cell hybrids, gene mapping, inherited genetic syndromes)
- Normal, Abnormal and Neoplastic States of Growth (e.g., cell growth cycle, fast growing vs slow growing)
- Normal and Neoplastic Cell Behavior (e.g., cell-cell adhesions, cell movement and migration-microtubules-microfilaments, cell-cell communication)
- Membrane Synthesis, Structure, Composition and Function (e.g., transport, receptors, sugar transferases, glycolipids, glycoproteins, basement membrane, extracellular matrix, gap junctions, tight junctions)
- Cell Metabolism - Regulation of (e.g., energy metabolism, metabolic pathways, enzymes, cGMP, cAMP)
- Nucleic Acid and Protein Synthesis and Processing, Interactions and Modifications - Regulation of (e.g., DNA, rRNA, sRNA, mRNA, regulation of gene expression, histones, nonhistones, chromatin)
- Nutritional, Hormonal and Protein Factor Requirements for Tumor Growth, Maintenance and Differentiation (e.g., cellular factors, serum factors, peptide hormones, steroid hormones)
- Model Systems for Studying Tumor Growth, Invasiveness and Metastasis

EXCEPTIONS AND QUALIFICATIONS:

Excluded from this program are all research studies focused on breast cancer detection and diagnosis and immunology. Also excluded are those studies oriented primarily to cancer therapy.

Experimental studies with prokaryotic and plant systems are supported only when these studies are clearly defended in terms of potential knowledge that will enhance cancer research. Except for comparative studies of normal and virally transformed cells in culture, this program is not concerned with the occurrence, nature or mechanism of action of virally induced cancers.

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REFERENCES

Azizkhan, R., Azizkhan, J., Zetter, B. and Folkman, J., "Mast Cell Heparin Stimulates Migration of Capillary Endothelial Cells in vitro", J. Exp. Med. 152: 931-944, 1980. (CA 14019)

Blackman, M.R., Weintraub, B.D., Rosen, S.W., Kourides, I.A., Steinwascher, K. and Gail, M.H., "Human Placental and Pituitary Glycoprotein Hormones and Their Subunits as Tumor Markers: A Quantitative Assessement," JNCI, 65:81-93, 1980. (CA 23185)

Bolmer, S.D., and Davidson, E.A., "Preparation and Properties of a Glycoprotein Associated with Malignancy", Biochemistry, in press, 1981. (CA 15483)

Brouty-Boye, D. and Zetter, B., "Inhibition of Cell Motility by Interferon", Science 208:516-518, 1980. (CA 28540)

Cairns, J., "The Origin of Human Cancers", Nature, 289: 353-357, 1981.

Croce, C.M., "Cancer Genes in Cell Hybrids", Biochim. et Biophys. Acta, 605:411-430, 1980. (CA 20741, CA 23568)

Fenselau, A. and Mello, R.J., "Growth Stimulation of Cultured Endothelial Cells by Tumor Cell Homogenates", Cancer Res. 36:3269-3273, 1976. (CA 15381)

Fenselau, A., Watt, S. and Mello, R.J., "Tumor Angiogenic Factor: Purification from the Walker 256 Rat Tumor", J. Biol. Chem., in press, 1981. (CA 15381)

Folkman, J., Haudenschild, C.C. and Zetter, B., "Long-term Culture of Capillary Endothelial Cells", Proc. Natl. Acad. Sci., U.S.A., 76:5217-5221, 1979. (CA 14019)

Folkman, J. and Haudenschild, C., "Angiogenesis in vitro", Nature 288:551-556, 1980. (CA 14019)

Folkman, J., Merler, E., Abernathy, C. and Williams, G., "Isolation of a Tumor Factor Responsible for Angiogenesis", J. Exp. Med. 133:275-288, 1971. (CA 14019)

Fox, J.L., "Cancer Researchers Identifying Common Clues", Chemical and Engineering News, pp. 16-20, March 16, 1981. (CA 08964, CA 14454 & CA 15823)

Kuettner, K.E. and Pauli, B.U., "Resistance of Cartilage to Invasion" in Bone Metastasis, eds. Gilbert, H.A., Weiss, L. and Monsen, D.C.G. (G.K. Hall & Co., Boston), pp. 131-165, 1981. (CA 21566)

Langan, T., "Malignant Transformation and Protein Phosphorylation", Nature 286: 329-330, 1981. (CA 12877)

Langer, R., Conn, H., Vacanti, J., Haudenschild, C. and Folkman, J., "Control of Tumor Growth in Animals by Infusion of an Angiogenesis Factor", Proc. Natl. Acad. Sci., U.S.A., 77:4331-4335, 1980. (CA 14019)

Linnenback, A., Huebner, K. and Croce, C.M., "DNA-transformed Murine Teratocarcinoma Cells: Regulation of Expression of Simian Virus 40 Tumor Antigen in Stem Versus Differentiated Cells", Proc. Natl. Acad. Sci., U.S.A., 77:4875-4879, 1980. (CA 20741, CA 21069)

Martin, G.R., Epstein, C.J., Travis, B., Tucker, G., Yatziv, S., Martin, D.W., Jr., Clift, S. and Cohen, S., "X-Chromosome Inactivation During Differentiation of Female Teratocarcinoma Stem Cells in vitro", Nature 271:329-333, 1978. (CA 25966)

Mintz, B., Illmensee, K. and Gearhart, J.D., "Developmental and Experimental Potentialities of Mouse Teratocarcinoma Cells from Embryoid Body Cores" in Teratomas and Differentiation, eds. Sherman, M.I. and Solter, D., (Academic, N.Y.), 1975.

Moscatelli, D., Jaffe, E. and Rifkin, D.B., "Tetradecanoyl Phorbal Acetate Stimulates Latent Collagenase Production by Cultured Endothelial Cells", Cell 20:343-351, 1980. (CA 23753)

Orr, W., S.H. Phan, J. Varani, P.A. Ward, D.L. Kreutzer, R.O. Webster, P.M. Henson, "Chemotactic Factor for Tumor Cells Derived from the C5a Fragment of Complement Component C5," Proc. Natl. Acad. Sci., U.S.A., 76:1986-1989, 1979. (CA 29551, CA 29550)

Oshima, R., McKerros, J. and Cox, D., "Murine Embryonal Carcinoma Hybrids: Decreased Ability to Spontaneously Differentiate as a Dominant Trait", J. Cell Physiol., in press, 1981. (CA 27580)

Papaioannou, V.E., McBurney, M.W. and Gardner, R.O., "Fate of Teratocarcinoma Cells Injected into Early Mouse Embryos, Nature (London) 258:70-73, 1975.

Pauli, B.U., S.N. Anderson, V.A. Memoli, and K.E. Kuettner, "Development of an in Vitro and in Vivo Epithelial Tumor Model for the Study of Invasion," Cancer Research, 40:4571-4580, 1980. (CA 21566)

Pierce, G.B., "Model for a Developmental Concept of Cancer", Current Topics Develop. Biol. 2:223-246, 1967. (CA 15823)

Pierce, G.B., Lewis, S.H., Miller, G.J., Moritz, E. and Miller, P., "Tumorigenicity of Embryonal Carcinoma as an Assay to Study Control of Malignancy by the Murine Blastocyst", Proc. Natl. Acad. Sci., U.S.A., 76:6649-6651, 1979. (CA 15823)

Podolsky, D.K. and Isselbacher, K.J., "Cancer-Associated Galactosyltransferase Acceptor", Cancer, 45: 1212-1217, 1980. (CA 14294)

Rigby, P.W.J., "The Detection of Cellular Transforming Genes", Nature 290: 186-187, 1981. (CA 28946)

Rosenstraus, M.J., Balint, R.F. and Levine, A.J., "Pluripotency of Somatic Cell Hybrids Between Nullipotent and Pluripotent Embryonal Carcinoma Cells", Somatic Cell Genetics 6:555-565, 1980. (CA 26014, CA 28106)

Rosenstraus, M.J. and Levine, A.J., "Alterations in the Developmental Potential of Embryonal Carcinoma Cells in Mixed Aggregates of Nullipotent and Pluripotent Cells", Cell 17:337-346, 1979. (CA 26014, CA 28106)

Stevens, L.D., "Genetic Influences on Teratocarcinogenesis in Mice" in A Century of Mammalian Genetics and Cancer, View in Midpassage, ed. Russell, E.S., (Alan R. Liss, Inc., N.Y.), pp. 1929-2029, in press, 1981 . (CA 02662)

Wass, J.A., J. Varani, P.A. Ward, "Size Increase Induced in Walker Ascites Cells by Chemotactic Factors," Cancer LeHers, 9:313-318, 1980. (CA 29551, CA 29550)

Weinhouse, S., "New Dimensions in the Biology of Cancer", Cancer, 45:2975-2980, 1980. (CA 10916)

Zetter, B.R., "Migration of Capillary Endothelial Cells is Stimulated by Tumour-derived Factors", Nature 285:41-43, 1980. (CA 28540)

R01-CA-02758 Steroid Metabolism in Tumors and Normal Tissues
Kandutsch Jackson Laboratory

R01-CA-08759 Structure, Biosynthesis and Function of Glycoproteins
Kornfeld Washington University

R01-CA-10917 Phosphate Transport and Metabolism in Carcinoma Cells
Levinson University of Texas Hlth. Sci. Ctr. San Antonio

R01-CA-12150 Unusual Lipids in Cancer Tissues
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R01-CA-12306 Preparation of Cancer Chemotherapy Abstracts, Volume XI
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R01-CA-12753 Cell Surfaces and Cells Transformed by Oncogenic Viruses
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R01-CA-12790 Substrate and Cation Transport in Human Leukocytes
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R01-CA-12920 Mechanisms of Intercellular Adhesion
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R01-CA-13402 Surface Membranes in Normal and Cancer Cells
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R01-CA-13605 Chemistry and Measurement of Intracellular Adhesion
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R01-CA-14370 Specificity of Normal and Cancer Cell Interactions
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R01-CA-14431 Cell Adhesion of Normal and Malignant Liver Cells
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R01-CA-14464 A Program on the Etiology and Diagnosis of Cancer
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R01-CA-14496 Metal Ion Activation of Concanavalin A
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R01-CA-14551 Penetration of Macromolecules into Mammalian Cells
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R01-CA-14609 Molecular Basis of Cellular Adhesiveness
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R01-CA-15483 Biochemistry of Mucopolysaccharides
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R01-CA-16335 Cell Junction Formation and Role in Cell Proliferation
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R01-CA-16777 The Biosynthesis of Cell Envelope Glycoproteins
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R01-CA-16856 Analysis of Eucaryotic Cell Surfaces
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R01-CA-17007 Cell Surface Structure and Transformation
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Warren Wistar Institute of Anatomy and Biology

R01-CA-19144 Membrane Changes Caused by Tumor Virus Transformation
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R01-CA-19158 Mammalian Collagenase in Tumor Invasion
Biswas Massachusetts General Hospital

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R01-CA-21463 Pathobiology of the Cell Membrane in Cancer
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Galbraith		Medical University of South Carolina
R01-CA-27285	Plasma Membranes and Control of Cell Growth	
Peterson		Boston University
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R01-CA-27397	Plasma Membrane Alterations in Transformed Cells	
Fink		University of Colorado Hlth. Sciences Ctr.
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Brysk		University of Texas Med. Br. Galveston
R01-CA-27455	Fibroblast Surface Antigen	
Ruoslahti		La Jolla Cancer Research Foundation
R01-CA-27460	Alpha-Fetoprotein: Structure and Function	
Ruoslahti		La Jolla Cancer Research Foundation
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Johnson		Kansas State University
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Culp		Case Western Reserve University
R01-CA-28101	Glycosaminoglycans in Normal and Malignant Cells	
Ruoslahti		City of Hope National Medical Center

R01-CA-28287	Driving Forces for Nutrient Transport in Tumor Cells	
Smith	University of Texas Hlth. Sci. Ctr. San Antonio	
R01-CA-28548	Developing Immunological Probes for Gap Junctions	
Johnson	University of Minnesota of Minneapolis-St. Paul	
R01-CA-28685	Phosphorylation Events and Transformed Cell Membranes	
Gordon	University of Colorado Hlth. Sciences Ctr.	
R01-CA-28867	Cell Surface Studies of Metastatic Melanoma	
Nicolson	University of Texas System Cancer Center	
R23-CA-29172	Structure and Function of the 170K Glycoprotein	
Carter	Fred Hutchinson Cancer Research Center	
R01-CA-29271	Pathobiology of Pancreatic Acinar Cell Carcinoma	
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R23-CA-29814	Noncytolytic Extraction of Tumor Antigens with Butanol	
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R01-CA-29995	Pathobiology of Malignant Cell Basement Membrane	
Furcht	University of Minnesota of Minneapolis-St. Paul	
R23-CA-30030	Sodium Ion Fluxes and Mitogenic Signaling	
Smith	University of Alabama in Birmingham	
R01-CA-30117	Epithelial-Mesenchymal Interaction in Endocrine Tissues	
Reid	Yeshiva University	
R01-CA-30231	Murine T Lymphocyte Cell Surface Antigens	
Springer	Harvard University	
R01-CA-30289	Human Epithelial Cells-Extracellular Matrix Interactions	
Vlodavsky	Hebrew University of Jerusalem	
R01-CA-30381	Study of the Plasma Membrane Matrix of Lymphoid Cells	
Mescher	Harvard University	
R01-CA-30538	Interactions of Platelets and Tumors Cells	
Jamieson	American National Red Cross	
R01-CA-30645	Glycosylation Mutants of Animals Cells	
Stanley	Yeshiva University	
R23-CA-31004	Cell-Substratum Interactions	
Barnes	University of Pittsburgh	
R01-CA-31103	Molecular Determinants of Multicellular Organization	
Hixson	University of Texas System Cancer Center	
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Carraway	University of Miami	

R01-CA-31761 Cell Surface Sugars in Pathogenesis and Therapy of CML
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ENZYMES

R01-CA-04679 Biology of Normal and Malignant Melanocytes
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R01-CA-10916 Metabolism of Normal and Neoplastic Tissue
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R01-CA-11655 Studies of Leukocyte Metabolism
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R01-CA-11949 Ether Lipids in Cancer-Enzyme Mechanisms and Inhibitors
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R01-CA-12563 Mechanism of Enzyme Induction by Cyclic Nucleotides
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R01-CA-14881 Regulation of Tyrosine Synthesis in Hepatoma Cells
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R01-CA-15196 Regulation of Fatty Acid Biosynthesis in Mammary Tumors
Ahmad Papanicolaou Cancer Research Institute

R01-CA-15979 Cholesterol Metabolism in Normal and Malignant Liver
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R01-CA-16184 Regulation of Enzyme Levels in Mouse Hepatoma
Felder University of South Carolina at Columbia

R01-CA-16231 Role of Collagenases in Tumor Invasion and Metastasis
Liener University of Minnesota at Saint Paul

R01-CA-21967 Fundamental Enzymologic Studies Applied to Oncology
Fishman La Jolla Cancer Research Foundation

R01-CA-22409 Enzyme Regulation in Normal and Neoplastic Cells
Deuel Jewish Hospital of St. Louis

R01-CA-22690 Cyclic Nucleotides in Cancer and Regenerating Tissue
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R01-CA-22717 Regulation of Folate Poly-Y Glutamate Synthesis
Shane Johns Hopkins University

R01-CA-23391 Cyclic GMP System in Cell Proliferation
Shoji Emory University

R01-CA-23533 Tumor Immunology: Phosphatase Isoenzymes
Doellgast Wake Forest University

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R01-CA-24966	Catalase Isozymes in Normal and Neoplastic Tissues	
Nishimura	U.S. PHS Hospital	
R01-CA-25005	The Regulation of Mammalian Enzyme Synthesis	
Greengard	Mount Sinai School of Medicine	
R01-CA-25088	Human Pancreatic Ribonuclease and Cancer	
Glitz	University of California Los Angeles	
R01-CA-25337	Drugs and Flavoprotein Mediated Superoxide Formation	
Powis	Mayo Foundation	
R01-CA-25473	Cyclic AMP Metabolism in Cultured Epithelial Cells	
Niles	Boston University	
R01-CA-25617	The Collagenolytic System of Invasive Tumors	
Dabbous	University of Tenn. Center Health Scien.	
R01-CA-26033	White Blood Cell Function in Hematologic Disorders	
Nathan	Children's Hospital Medical Center	
R01-CA-26102	Protein Kinase System in Rapidly Growing Hepatomas	
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R01-CA-26470	Regulation of Dihydrofolate Reductase Gene Expression	
Johnson	Ohio State University	
R01-CA-26546	Regulation of Enzyme Activity in Normal and Tumor Cells	
Canellakis	Yale University	
R01-CA-27073	Cellular Enzyme Changes in Childhood Leukemia	
Dunn	Virginia Commonwealth University	
R01-CA-27491	Form and Function of Normal and Neoplastic Ferritins	
Massover	College of Medicine and Dentistry of NJ	
R23-CA-27500	The Control of Cyclic GMP in Human Lymphocytes	
Takemoto	Kansas State University	
R01-CA-27572	Ribonucleotide Reductase of Tumor Cells	
Cory	University of South Florida	
R01-CA-27674	Control of Pyrimidine Biosynthesis in Mammalian Cells	
Evans	Wayne State University	
R01-CA-28111	Hormonal Regulation of Kidney Epithelial Cell Growth	
Taub	University of California San Diego	
R01-CA-28376	Nucleotide Biosynthesis and Degradation	
Silber	New York University	

R01-CA-28725 Asparagine Biosynthesis in Normal and Tumor Cells
Schuster University of Nebraska Lincoln

R01-CA-28781 Dolichyl Phosphate Biosynthesis in Tumor Cells
Adair University of South Florida

R23-CA-28973 A Cell Culture Model for Regulation of Tumor Cell Growth
Epstein Children's Hospital Medical Center

R01-CA-29187 Characterization of a Novel Rat Lactate Dehydrogenase
Anderson University of Pittsburgh

R01-CA-29307 Control of Protease Action on Human Cells
Baker University of Kansas Lawrence

PEPTIDE HORMONES

R01-CA-02146 Cytoplasmic Factors in Cellular Growth
Bucher Massachusetts General Hospital

R01-CA-07535 Control of Pituitary Gland and Pituitary Tumor Hormones
Macleod University of Virginia

R01-CA-11685 Tumor Cell Synthesis and Secretion of Peptide Hormones
Orth Vanderbilt University

R01-CA-16417 Pituitary Hormones in Normal and Neoplastic Growth
Ramachandran University of California San Francisco

R01-CA-17309 Prostaglandins and Enzymes in Normal and Malignant Tissues
Levine Brandeis University

R01-CA-18406 Histaminase and Amines in Neural Crest Tumors
Baylin Johns Hopkins University

R01-CA-19234 Extrinsic Fluorescence and Membrane Potentials
Laris University of California Santa Barbara

R01-CA-22394 Hormonal Control of Cell Proliferation
Thompson University of South Carolina at Columbia

R01-CA-23185 Regulation of Alpha and Beta Subunits of TSH
Kourides Sloan Kettering Institute for Cancer Res.

R01-CA-24050 ACTH Secretion by Pituitary Tumor Cells in Culture
Richardson Harvard University

R01-CA-24604 Triiodothyronine Receptors and Nonthyroidal Diseases
Surks Montefiore Hospital and Medical Center

R01-CA-25614 Antiestrogen Action and Cancer
Williams Worcester Fdn. for Exper. Biology

R01-CA-25820 Receptors and Growth Factors for Neoplastic Cells
Schlessinger Weizmann Institute of Science

R01-CA-28218 Hormone Production by Pituitary Tumor Cells
Biswas Harvard University

R01-CA-28826 Mutations Affecting Gene Expression in Tumor Cells
Ivarie University of Georgia

R01-CA-29467 The Biochemistry of Cellular Transformation
Vanaman Duke University

R01-CA-29808 Molecular Mechanism of Desensitization
Iyengar Baylor College of Medicine

R01-CA-30253 A Study of Tropic Hormone Action in Carcinoma Cells
Mason University of Texas Hlth. Sci. Ctr. Dallas

R01-CA-30388 Humoral Regulation of Normal and Malignant Hemopoiesis
Golde University of California Los Angeles

R01-CA-30393 Endocrine Regulation of Melanoma Cell Differentiation
Fuller Texas Tech University

STEROIDS

R01-CA-08315 Steroid Induced Changes in Cultured Malignant Cells
Melnykovych University of Kansas

R01-CA-13103 Metabolism and Inhibition of Prostatic Neoplasia
Mawhinney West Virginia University

R01-CA-13410 Mechanism of Hormone Action on Target Cells in Culture
Sonnenschein Tufts University

R01-CA-16091 Biochemical Control in Adrenocortical Carcinoma Cells
Sharma University of Tenn. Center Health Scien.

R01-CA-17229 Keloids: An In Vitro Model of Tumor Growth Regulation
Russell Meharry Medical College

R01-CA-17323 Glucocorticoid-Resistant Leukemic Lymphocytes
Munck Dartmouth College

R01-CA-19907 Physiology of Pituitary Cell Glucocorticoid Binding
Harrison Vanderbilt University

R01-CA-23248 Prolactin Cell Function in Breast Cancer
Hymer Pennsylvania State University Univ. Park

R01-CA-23603 Gonadotropin Actions in Leydig Tumor Cells
Ascoli Vanderbilt University

R01-CA-23921	Biochemical and Clinical Aspects of Steroid Receptors	
Colas		University of Wisconsin Madison
R01-CA-24228	Endocrine Factors in Cancer-Induced Lipolysis	
Zepp		Kirksville College of Osteopathic Med.
R01-CA-24347	Hormone Effects on Proliferation of Malignant Thymocytes	
Thompson		University of South Carolina
R01-CA-25365	Hormonal Regulation of Cultured Endometrial Cells	
Gerschenson		University of Colorado Hlth. Sciences Ctr.
R23-CA-25655	Protein Mediators of Lethal Glucocorticoid Effects	
Nicholson		University of Rochester
R01-CA-26020	Corticosteroids--Cytokinetic and Biochemical Studies	
Braunschweiger		Allegheny-Singer Research Corporation
R01-CA-26112	Effect of Estrogen on Normal and Abnormal Cell Growth	
Clark		Baylor College of Medicine
R01-CA-26617	Estrogen Mediated Pituitary Tumor Cell Growth	
Sirbasku		University of Texas Hlth. Sci. Ctr. Houston
R01-CA-26638	Cyclic AMP: Role in Adrenal Tumor Steroidogenesis	
Moyle		Rutgers Medical School
R01-CA-27702	Sex Hormones, Cancer and the Immune System	
Siiteri		University of California San Francisco
R01-CA-27828	Pituitary Steroid Receptors, Estrogens, and Adenomas	
Eisenfeld		Yale University
R23-CA-28580	Therapeutic Implications of Hormone in Nevi and Melanoma	
Chaudhuri		University of Illinois Medical Center
R01-CA-29324	Interactions of Estrogen Receptor with Chromatin	
Hilf		University of Rochester
R01-CA-29485	Actions of Estrogens and Antiestrogens in the Nucleus	
Kallos		Hospital for Joint Diseases Ortho Inst.
R01-CA-29497	An Adrenal Tumor: Cytochrome P-450 and Steroidogenesis	
Hall		Worcester Fdn. for Exper. Biology
R01-CA-30380	Glucocorticoid Suppression of Transformed Cell Growth	
Young		Boston University

MEMBRANOUS ORGANELLES

R01-CA-06576	Biological Effects of a Placental Protease Inhibitor	
Novikoff		Yeshiva University

R01-CA-08964	Energy Metabolism in Normal and Tumor Cells	
Racker		Cornell University
R01-CA-10951	Control of Enzymatic Phosphate Transfer in Mitochondria	
Pedersen		Johns Hopkins University
R01-CA-11766	Metabolic Regulation in Neoplasms by Cation Transport	
Cockrell		St. Louis University
R01-CA-12312	Mitochondrial Gene Expression in Malignant Cells	
Clayton		Stanford University
R01-CA-12858	Lysosome Biogenesis: Normal and Tumor Cells	
Stahl		Washington University
R01-CA-13814	Mitochondrial Genetic System in Normal and Cancer Cells	
Nass		University of Pennsylvania
R01-CA-16527	Regulation of Mitochondrial DNA	
Robberson		University of Texas Cancer Center
R01-CA-20454	Adenine Nucleotide Translocation in Tumor Mitochondria	
Chan		Syracuse University Syracuse
R01-CA-22031	Trans-membrane Control in Transformed and Normal Cells	
Singer		University of California San Diego
R01-CA-25360	Respiration-Coupled Transport Processes in Tumor Cells	
Lehninger		Johns Hopkins University
R01-CA-27117	A Study of Membrane Bound ATPases of Human Tumors	
Knowles		University of California San Diego
R01-CA-28677	Transport in Cholesterol-Rich Tumor Mitochondria	
Coleman		New York University

RIBOSOMES

R01-CA-04186	Molecular Structure of Nucleic Acids and Proteins	
Rich		Massachusetts Institute of Technology
R01-CA-08416	Transcription and Translation in Mammalian Cells	
Penman		Massachusetts Institute of Technology
R01-CA-16608	Translation Control in Reticulocytes and Leukemic Cells	
Hardesty		University of Texas Austin
R01-CA-21663	Intermediary Metabolism in Animals and in Man	
Henshaw		University of Rochester
R01-CA-23632	RNA Methylation: A Paradox in Normal and Cancer Cells	
Sitz		Old Dominion University

R01-CA-25618 rDNA-Binding Proteins and Control of rDNA in Tumors
Bearden University of Hawaii at Manoa

R01-CA-28513 Structure of Hypomethylated Tumor 5.8S Ribosomal RNA
Lightfoot Eastern Washington University

M-RNA

R01-CA-12550 RNA Synthesis and Transport in Mammalian Cells
Martin University of Chicago

R01-CA-13175 Control of RNA Processing in Normal and Tumor Cells
Bottman Michigan State University

R01-CA-17287 Aspects of Control in Mammalian Gene Expression
Stark Stanford University

R01-CA-18065 Biogenesis of Messenger RNA in Animal Cells
Edmonds University of Pittsburgh

R01-CA-19535 Structure of Nuclear RNA and Messenger RNA Formation
Molloy University of Delaware

R01-CA-22302 Analysis of Gene Regulation by Nuclear Transplantation
Lucas State University New York Stony Brook

R01-CA-23226 Gene Expression in Regenerating and Neoplastic Livers
Fausto Brown University

R01-CA-24165 Hemoglobin Studies in Friend Leukemia
Zucker Papanicolaou Cancer Research Institute

R01-CA-24206 Embryonal Carcinoma Growth and Differentiation
Linney La Jolla Cancer Research Foundation

R01-CA-24273 Expression of Globin Genes--Erythroleukemia Cells
Rovera Wistar Institute of Anatomy and Biology

R01-CA-24635 Chromosomal Manifestations of Gene Expression
Melera Sloan Kettering Institute for Cancer Res.

R01-CA-25078 Poly(A) Polymerases from Liver and Hepatomas
Jacob Pennsylvania State Univ. Hershey Med. Ctr.

R01-CA-26073 Mapping Globin Sequences in Nuclear Ribonucleoprotein
Augenlicht Sloan Kettering Institute for Cancer Res.

R01-CA-26790 Phenotypic Variation and Neoplastic Progression
Peterson Children's Hospital Med. Ctr. Northern Ca.

R01-CA-27932 Developmentally Regulated Genes in Teratocarcinoma
Solter Wistar Institute of Anatomy and Biology

R01-CA-28555	Neoplastic Activation of Fetal Gene Expression	
Hoch		Scripps Clinic and Research Foundation
R01-CA-30124	Role of 2-5A in Growth Arrest and Hormone Responses	
Stark		Stanford University
R01-CA-30151	Regulation of Albumin Synthesis by Amino Acids	
Ledford		Medical University of South Carolina

T-RNA

R01-CA-10922	Metabolism of Animal Cell Ribosomes	
Vaughan		University of Pittsburgh
R01-CA-20683	Control Mechanisms in Human Tumor Cells--Small RNAs	
Eliceiri		St. Louis University
R01-CA-20919	tRNA Q-Base: Its Relation to Differentiation	
Katze		University of Tenn. Center Health Scien.
R01-CA-21245	Structure and Modification of Mammalian Transfer RNA	
Penhoet		University of California Berkeley
R01-CA-23363	tRNA Methylation in Mammalian Cells	
Leboy		University of Pennsylvania
R01-CA-23536	Molecular Biology of Ethionine Carcinogenesis	
Borek		AMC Cancer Research Center and Hospital
R01-CA-24727	Changes in RNA Metabolism and the Induction of Tumors	
Apirion		Washington University
R01-CA-26423	Modification of tRNA 1/4YS Controls Cell Proliferation	
Ortwerth		University of Missouri Columbia
R01-CA-27235	tRNA Modification and Gene Expression in Mammalian Cells	
Hatfield		University of California Irvine
R01-CA-27288	Regulation of Gene Expression in Human Tumor Cells	
Eliceiri		St. Louis University
R01-CA-28053	Thiolated tRNAs in Rat Liver and Morris Hepatomas	
Wong		University of Chicago
R01-CA-28395	tRNA Methylation in Normal and Neoplastic Rat Tissues	
Leboy		University of Pennsylvania

R01-CA-14835 DNA Polymerases in Normal and Neoplastic Human Cells
Korn Stanford University

R01-CA-15044 Pathogenetic Determinants of Human CNS Tumors
Manuelidis Yale University

R01-CA-15187 DNA Synthesis: Regulation in Normal and Cancer Cells
Baril Worcester Fdn. for Exper. Biology

R01-CA-16790 DNA Transcription Control in Normal and Cancer Cells
Maio Yeshiva University

R01-CA-17723 Regulation of DNA Synthesis in the Novikoff Hepatoma
Meyer University of Cincinnati

R01-CA-18138 Mammalian Polyamine Metabolism
Pegg Pennsylvania State Univ. Hershey Med. Ctr.

R01-CA-18564 Chediak-Higashi and Cancer Cells with Similar Defects
Oliver University of Connecticut Health Center

R01-CA-22610 Cytoskeleton and Cell Transformation to Malignancy
Brinkley Baylor College of Medicine

R01-CA-23365 Function of DNA Polymerases in Normal and Cancer Cells
Chang U.S. Uniformed Services Univ. of Health Sciences

R01-CA-24151 Regulation of Cell Growth by 5'-Methylthioadenosine
Vandenbark University of Oregon Hlth. Sciences Ctr.

R01-CA-24158 DNA Synthesis in Transformed Cells
Collins Virginia Commonwealth University

R01-CA-24323 DNA Precursor Dynamics in Animals Cells
Mathews Oregon State University

R01-CA-24845 The Fidelity of DNA Replication in Human Lymphocytes
Loeb University of Washington

R01-CA-25023 Inhibitor of DNA Polymerase Produced by Tumor Cells
Gottlieb Tulane University of Louisiana

R01-CA-26391 Molecular Pathology of Leukemia and Lymphoma
Coleman University of Kentucky

GROWTH FACTORS

R01-CA-11176 Factors Required for Mammalian Cell Division
Holley Salk Institute for Biological Studies

R01-CA-13808	Transformation and Recovery of Crown Gall Tumor Cells	
Wood		Rockefeller University
R01-CA-14019	Tumor Angiogenesis: A Control Point in Tumor Growth	
Folkman		Children's Hospital Medical Center
R01-CA-17203	Role of Serum and Cations in Malignant Cell Growth	
Tupper		Syracuse University
R01-CA-17620	Growth Control in Normal and Neoplastic Cells	
Smith		University of Nebraska Lincoln
R01-CA-19275	Normal and Leukemic Granulopoiesis	
Dodge		Wake Forest University
R01-CA-19731	Hormonal Requirement of Cells In Vitro and In Vivo	
Sato		University of California San Diego
R01-CA-21763	Growth Control by a Mitogen Purified from Cartilage	
Klagsbrun		Children's Hospital Medical Center
R01-CA-22410	Copper Absorption and Ceruloplasmin in Cancer	
Linder		California State University Fullerton
R01-CA-23528	Inhibitory Interactions Regulating Hematopoiesis	
Broxmeyer		Sloan Kettering Institute for Cancer Res.
R01-CA-24395	Fibroblast Growth Factors and Phosphorylation	
Nilson-Hamilton		Salk Institute for Biological Studies
R01-CA-27031	Maturation Factors and Cancer Cells	
Lim		University of Chicago
R01-CA-27113	Molecular Analysis of Platelet-Derived Growth Factor	
Scher		Sidney Farber Cancer Institute
R01-CA-27217	Growth Factors and Receptors in Chemical Transformation	
Moses		Mayo Foundation
R23-CA-27802	Pharmacologic Modulation of Erythroid Colony Formation	
Beckman		Tulane University of Louisiana
R01-CA-28110	Nerve Growth Factor: Secretion by Cancer Cells	
Young		University of Florida
R01-CA-28456	Biochemical Mechanisms of Cellular Invasion	
Rifkin		New York University
R01-CA-28540	Growth and Migration of Capillary Endothelial Cells	
Zetter		Children's Hospital Medical Center
R01-CA-28638	Altered Nutritional Requirements for Growth	
Topp		Cold Spring Harbor Laboratory

R01-CA-28858	Biological and Synthetic Modulators of Cell Growth	
Pickart		Virginia Mason Research Center
R01-CA-29101	Characterization of a Liver Specific Growth Promoter	
LaBrecque		University of Iowa
R01-CA-30101	Structure and Function of Platelet-Derived Growth Factor	
Antoniades		Center for Blood Research
R01-CA-30479	Mononuclear Phagocyte-Derived Growth Regulating Factors	
Gillespie		University of North Carolina Chapel Hill
R01-CA-30536	New Myeloid Hemapoietins: Normal and Leukemic Marrow	
Wells		University of California Los Angeles

NUCLEUS

R01-CA-10872	Interactions of Chromosomal Proteins	
Isenberg		Oregon State University
R01-CA-12226	Protein Methylation in Neoplastic Tissue	
Paik		Temple University
R01-CA-12877	Function of Lysine Rich (H1) Histone Phosphorylation	
Langan		University of Colorado Hlth. Sciences Ctr.
R01-CA-13195	Histone ADP-Ribosylation and HeLa Cell Replication	
Smulson		Georgetown University
R01-CA-15135	Histones in Cell Differentiation and Carcinogenesis	
Zweidler		Fox Chase Cancer Center
R01-CA-15923	Nonhistone Proteins of Reactivated Erythrocyte Nuclei	
Shelton		Virginia Commonwealth University
R01-CA-16910	Chromosome Aberrations in Myeloproliferative Diseases	
Rowley		University of Chicago
R01-CA-17782	Tumor-Enriched Nonhistone Chromatin Proteins	
Reeck		Kansas State University
R01-CA-18389	Proteins of the Cell Nucleus	
Hnilica		Vanderbilt University
R01-CA-18455	Isolated Chromosomes in Genetics and Cancer Research	
Wray		Baylor College of Medicine
R01-CA-21927	Chromatin Structure of Normal and Malignant T-Cells	
Maizel		University of Texas Cancer Center
R01-CA-24546	Relation of Histones to DNA in Normal and Cancer Cells	
Kornberg		Stanford University

R01-CA-25055	Cytogenetics of Clonal Neoplasias	
Hecht		Southwest Biomedical Research Institute
R01-CA-25735	Regulatory Processes Biochemistry in Synchronized Cells	
Hodge		Medical College of Georgia
R01-CA-27446	Nuclear Proteins in Hepatoma and Normal Liver	
Ruoslahti		La Jolla Cancer Research Foundation
R01-CA-27661	Sister Chromatid Exchange in ALL	
Palmer		Indiana Univ.-Purdue Univ. at Indianapolis
R01-CA-28168	Cytogenetics of Hepatocellular Carcinoma in Nigeria	
Cervenka		University of Minnesota of Minneapolis-St. Paul
R01-CA-28679	Chromosomal Organization of Dihydrofolate Reductase Gene	
Biedler		Sloan Kettering Institute for Cancer Res.
R01-CA-29340	rDNA Distribution in Chromosomes of Neoplastic Cells	
Henderson		Columbia University
R01-CA-29476	Clonal Karyotypic Evolution in Human Solid Tumors	
Trent		University of Arizona
R01-CA-29617	Role of Double Minutes and HSR Markers in Tumor Cells	
George		Johns Hopkins University
R01-CA-29779	DNA Replication: Chromosomes and Neoplasms	
Cervenka		University of Minnesota of Minneapolis-St. Paul
R01-CA-31024	Fine Structural Chromosomal Defects in Acute Leukemia	
Yunis		University of Minnesota of Minneapolis-St. Paul

CONTRACTILE ELEMENTS

R01-CA-05493	Leukopoietic Mechanisms	
De Bruyn		University of Chicago
R01-CA-15229	Actin and Tubulin Cancer Cells	
Weihing		Worcester Fdn. for Exper. Biology
R01-CA-15544	Effect of Microtubular Proteins on Cell Surfaces	
Berlin		University of Connecticut Health Center
R01-CA-20836	Cytochalasins and Cell Membrane Contractile Apparatus	
Godman		Columbia University
R01-CA-26473	ACTH Effects of the Cytoskeleton of Adrenal Tumor Cells	
Mattson		Case Western Reserve University
R01-CA-26867	Invasion and Metastasis	
Zeidman		University of Pennsylvania

R01-CA-27458 Biochemistry of Cytoskeletal Proteins
Tuszynski Temple University

R01-CA-28362 Levels of Metastasis Inhibition in Primary Cancers
Rapp Roswell Park Memorial Institute

R01-CA-29985 Microtubules and Nonmicrotubular Aggregates
Weisenberg Temple University

R01-CA-30085 Immune Mechanism in Cells Initiating ERV Production
Albrecht-Buehle Cold Spring Harbor Laboratory

DEVELOPMENT AND DIFFERENTIATION

R01-CA-02662 Investigations of Teratocarcinogenesis
Stevens Jackson Laboratory

R01-CA-08482 Differentiation and Function of Hematopoietic Cells
Scott Virginia Commonwealth University

R01-CA-10095 Gene Action and Cellular Differentiation in Culture
Silagi Cornell University Medical Center

R01-CA-12187 Growth and Differentiated Function in Mammalian Cells
Green Massachusetts Institute of Technology

R01-CA-13047 Control Mechanisms of Differentiation and Malignancy
Friend Mount Sinai School of Medicine

R01-CA-13533 Ectopic Placental Proteins in Human Cancer
Sussman Stanford University

R01-CA-14319 Biological Functions of Plasma Membrane Sialidase
Schengrund Pennsylvania State Univ. Hershey Med. Ctr.

R01-CA-15222 Hepatoma Alpha-Fetoprotein: Chemistry and Metabolism
Smith University of Vermont and St. Agric. College

R01-CA-16368 Control of Differentiation of Erythroleukemic Cells
Skoultchi Yeshiva University

R01-CA-16746 Control of Albumin Synthesis in Liver and Hepatomas
Taylor Pennsylvania State Univ. Hershey Med. Ctr.

R01-CA-17389 C-Cell Hyperplasia and Thyroid Medullary Carcinoma
Wolfe Tufts University

R01-CA-17563 DNA Binding Proteins in Human Serum
Hoch Scripps Clinic and Research Fdn.

R01-CA-17575 Erythroid Differentiation in Friend Leukemia Cells
Housman Massachusetts Institute of Technology

R01-CA-18375 Hemopoietic Stem Cells and Induced Differentiation
Goldwasser University of Chicago

R01-CA-19492 Terminal Transferase in Mammalian Hemopoietic Tissue
Coleman University of Kentucky

R01-CA-20053 Tumor Inception and Progression
Meins University of Illinois Urbana-Champaign

R01-CA-21566 Antitumor Invasion Factors Derived from Cartilage
Kuettner Rush-Presbyterian-St. Luke's Medical Ctr.

R01-CA-22099 Alpha-Fetoprotein Synthesis by Hepatoma Cells In Vitro
Kelleher University of Vermont and St. Agric. College

R01-CA-22227 Onco-Developmental Gene Control: Alpha-Fetoprotein
Sell University of California San Diego

R01-CA-22294 Quantitative Studies on Granulocyte Differentiation
Kinkade Emory University

R01-CA-22556 Differentiation of Granulocytes and Monocytes
Burgess Walter and Eliza Hall Inst. Medical Res.

R01-CA-22558 Comparative Biochemistry of Cartilage Tumors
Oegema University of Minnesota of Minneapolis-St. Paul

R01-CA-22670 Control of Hemopoietic Stem Cell Differentiation
Trentin Baylor College of Medicine

R01-CA-22735 Thymic Modification of Leukemogenesis
Sensenbrenner Johns Hopkins University

R01-CA-23097 Embryo Derived Teratocarcinoma
Damjanov Hahnemann Med. Col. and Hosp. of Philadelphia

R01-CA-23615 Molecular Basis of Differentiation and Neoplasia
Roeder Washington University

R01-CA-24010 Differentiation of Cancer
Pierce University of Colorado Hlth. Sciences Ctr.

R01-CA-24241 Differentiation in a Malignant Neural Tumor
Sandquist University of Iowa

R01-CA-24479 Membrane Structure and Enzyme Induction
Chen Rutgers The State Univ. New Brunswick

R01-CA-25098 Alpha-Fetoprotein Regulation in Fetal and Cancer Liver
Chiu University of Vermont and St. Agric. College

R01-CA-25164 Malignant Phenotypes: Cytoplasmic and Nuclear Control
Sudilovsky Case Western Reserve University

R23-CA-25285	Ectopic Antigens in Hepatocellular Cancer	
Higgins		Sloan Kettering Institute for Cancer Res.
R01-CA-25512	Modulators of Granulopoiesis from Human Cell Lines	
Brennan		University of Rochester
R01-CA-25799	Conformation of Alpha-Fetoprotein Gene in Chromatin	
Anderson		Purdue University
R01-CA-25966	X-Chromosome Activity in Teratocarcinoma Stem Cells	
Martin		University of California San Francisco
R01-CA-25972	Leukemia Induction in Multipotential In Vitro Colonies	
Metcalf		Walter and Eliza Hall Inst. Medical Res.
R01-CA-25985	Response to Phagocytic Leukocytes to Tumor Promoters	
Christman		Mount Sinai School of Medicine
R01-CA-26014	Cell Interactions in Teratocarcinoma Differentiation	
Rosenstraus		Rutgers The State Univ. New Brunswick
R01-CA-26038	Study of Myeloid Leukemia Using Human Leukemia Lines	
Koeffler		University of California Los Angeles
R01-CA-26105	Human Renal Cancer and Hematopoiesis	
Sytkowski		Children's Hospital Medical Center
R01-CA-26234	Fibroblastic Colonies in Myeloproliferative Disorders	
Greenberg		University of California Davis
R23-CA-26401	Human Leukemia Marrow	
Fay		Duke University
R01-CA-26506	Myeloid Development in an Induced Leukemic Cell Line	
Cohen		Children's Hospital Medical Center
R01-CA-26656	Cell Culture Analysis of Human Epidermal Neoplasia	
Rheinwald		Sidney Farber Cancer Institute
R01-CA-26847	Regulation of mRNA Translation in Animal Cells	
Weber		University of South Florida
R01-CA-26993	Cytotoxic Factor(s) from Human Ovarian Adenocarcinoma	
Sheid		Downstate Medical Center
R01-CA-27287	Vaginal and Cervical Epithelial Cell Culture Model	
Rice		Harvard University
R01-CA-27466	Endothelial Colony-Stimulating Activity	
Quesenberry		University of Virginia
R01-CA-27580	Chromatin Proteins of Embryonal Carcinoma Cells	
Oshima		Massachusetts Institute of Technology

R01-CA-27682	New Technology for Classifying Human Leukemia	
Stang		University of California Los Angeles
R01-CA-28050	Regulation of Alpha-Fetoprotein Gene Expression	
Tilghman		Institute for Cancer Research
R01-CA-28106	Differentiation of Teratocarcinoma Cells	
Levine		State University of New York Stony Brook
R01-CA-28179	Lithium Effects on Hemopoietic Stem Cells	
Joyce		University of Pittsburgh
R01-CA-28228	Expansion of Hemopoietic Bone Marrow	
Lee		University of Washington
R23-CA-28289	Differentiation and Tumorigenicity in Recombinant Cells	
Moore		University of Colorado Hlth. Sciences Ctr.
R01-CA-28427	EGF and Its Receptors in Embryonic Differentiation	
Adamson		La Jolla Cancer Research Foundation
R23-CA-28512	Regulation of Normal and Leukemic Myeloid Stem Cells	
Pelus		Sloan Kettering Institute for Cancer Res.
R01-CA-28656	Differentiation of Capillary Endothelial Cells	
Auerbach		University of Wisconsin Madison
R01-CA-28815	Biosynthesis of Carcinoembryonic Antigen	
Mendicino		University of Georgia
R01-CA-29169	Gene Expression Embryonal Carcinoma Differentiation	
Linney		La Jolla Clinic Research Foundation
R01-CA-29895	Antiproliferative Effects of Interferons	
Baglioni		State University of New York at Albany
R01-CA-29959	Glycoproteins in Differentiation and Oncogenesis	
Fukuda		Fred Hutchinson Cancer Research Center
R01-CA-30049	Oncofetal Gene Regulation in Hepatocarcinogenesis	
Papaconstantino		University of Texas Med. Br. Galveston
R01-CA-30684	Regional Differences in Tumor Growth and Development	
Auerbach		University of Wisconsin Madison
R01-CA-31042	Developmental Regulation of E Globin Gene Expression	
Lo		University of Pennsylvania
R01-CA-31271	Differentiation and Stroma-Induction in Neural Tumors	
Rubinstein		University of Virginia
R01-CA-31777	Budr Dependence, Malignancy, and Differentiation	
Davidson		Children's Hospital Medical Center

R01-CA-06663	Repair of Chromatin by 3-Methyladenine N-Glycosylase	
Lieberman		University of Pittsburgh
R01-CA-08373	Study of Factors Controlling Cellular Proliferation	
Baserga		Temple University
R01-CA-15062	Studies of Normal and Neoplastic Prostate	
Ahmed		University of Minnesota of Minneapolis-St. Paul
R01-CA-15141	Control of Nuclear Events in Normal and Neoplastic Cells	
O'Neill		University of Utah
R01-CA-15305	Effect of Malignancy on Cell Growth Requirements	
Ham		University of Colorado at Boulder
R01-CA-15381	Control of Tumor Induced Angiogenesis	
Fenselau		Johns Hopkins University
R01-CA-15744	Primary Events in Regulating Cell Multiplication	
Rubin		University of California Berkeley
R01-CA-15813	Lipid Transport and Metabolism in Cancer-Host Systems	
Baker		University of California Los Angeles
R01-CA-16463	Triiodothyronine Receptors and Thyrotroph Neoplasia	
Surks		Montefiore Hospital and Medical Center
R01-CA-16816	Mechanism of Chemical Carcinogenesis In Vitro	
Moses		Mayo Foundation
R01-CA-19126	Cystine Auxotrophy in Human Malignancy--Implications	
Lazarus		Sidney Farber Cancer Institute
R01-CA-20136	Tumor Lipids: Metabolism and Structural Studies	
Wood		Texas Agri. and Mech. Univ. College Station
R01-CA-21359	Cell Interactions During Malignant Transformation	
Bertram		Roswell Park Memorial Institute
R01-CA-22011	Studies of Myeloid Leukemia in RFM Mice	
Trobaugh		Bush-Presbyterian-St. Luke's Medical Ctr.
R01-CA-22042	Role of Serum in the Foreign Body Response	
Stiles		Sidney Farber Cancer Institute
R01-CA-22088	Control of Growth in Quiescent Human Cells	
Norin		Montefiore Hospital and Medical Center
R01-CA-23022	Studies of Mitosis in Normal and Neoplastic Cells	
Brinkley		Baylor College of Medicine

R01-CA-24193 Pledger	Regulation of Mammalian Cell Cycle	University of North Carolina Chapel Hill
R01-CA-24385 Mastro	Effects of Phorbol Esters on Lymphocyte Stimulation	Pennsylvania State University Univ. Park
R01-CA-24914 Wolcott	Control of Cell Division in Leukemia Cells	Louisiana State Univ. Med. Ctr. Shreveport
R01-CA-24961 Castor	Protein Synthesis and Control of the Cell Cycle	Institute for Cancer Research
R01-CA-25009 Fahey	Role of Disulfides in Normal and Tumor Cell Growth	University of California San Diego
R01-CA-26070 Basilico	Control of Cycle Progression in Animal Cells	New York University
R01-CA-26081 Varga	Cell Cycle Dependence of Cell Surface Receptors	Yale University
R23-CA-26889 Frantz	Regulation of Cell Growth by Membrane Ion Flux	Sidney Farber Cancer Institute
R23-CA-26956 Neely	Detailed Cell Kinetic Analyses of Human Neuroblastoma	Children's Hospital Medical Center
R01-CA-27151 Reiter	Regulation of Cell Replication by Thymidine	University of Illinois Medical Center
R01-CA-27399 Sisken	Regulation of Mitosis in Normal and Transformed Cells	University of Kentucky
R01-CA-27419 Heppner	Immunopharmacologic Consequences of Tumor Heterogeneity	Michigan Cancer Foundation
R01-CA-27544 Rao	Purification and Characterization of Mitotic Factors	University of Texas System Cancer Center
R01-CA-27562 Litt	Regulation of Transfer RNA Levels in Mammalian Cells	University of Oregon Hlth. Sciences Ctr.
R01-CA-27564 Hoffman	Methionine Dependence--A Metabolic Marker in Cancer	University of California San Diego
R23-CA-27808 Tischler	Plasticity of Chromaffin and Pheochromocytoma Cells	Tufts University
R01-CA-27809 Sauer	Pathways of Energy Metabolism in Malignancy In Vivo	Mary Imogene Bassett Hospital
R01-CA-28140 Tryfiates	A Novel Vitamin B6 Metabolite in Hepatomas	West Virginia University

R01-CA-28238	Effects of Mitogens on Normal and Neoplastic Cells	
Vogel		University of Washington
R01-CA-28240	Pathology in Cell Cycle Control of Differentiation	
Scott		Mayo Foundation
R23-CA-28329	Phase Specific DNA Repair in Irradiated Tumor Cells	
Keng		University of Rochester
R01-CA-28519	Characterization of Cells and Clones from Human Brain	
Rosenblum		University of California San Francisco
R01-CA-28760	Anticoagulants, Vitamin K and Tumor Cell Growth	
Hauschka		Children's Hospital Medical Center
R01-CA-28803	The Role of AP4A in Malignant Transformation	
Rapaport		Boston University
R01-CA-28964	Tumor Cell-Vascular Endothelial Cell Interactions	
Birdwell		La Jolla Cancer Research Foundation
R01-CA-29560	Cyclic AMP Analogs as Growth Regulators in Tumor Cells	
Wicks		University of Tennessee Knoxville
R01-CA-30083	Aortic Growth Inhibitors	
Eisenst		Mount Sinai Medical Center
R01-CA-31053	Mitotic Inducing Protein (S) from Mammalian Cells	
Vogelstein		Johns Hopkins University

SOMATIC CELL GENETICS

R01-CA-12130	Cytoplasmic Inheritance in Normal and Tumor Cells	
Harris		University of California Berkeley
R01-CA-16631	Isolation and Analysis of DNA Mutants of BHK Cells	
Meiss		New York University
R01-CA-16720	Gene Regulation and Interaction--Normal and Malignant Cells	
Klinger		Yeshiva University
R01-CA-16754	Hybridization, DNA Function, Mutation in Cell Culture	
Littlefield		Johns Hopkins University
R01-CA-19401	Genetic Analysis of Human Malignancy	
Stanbridge		University of California Irvine
R01-CA-21054	Genetic Analysis of Malignant Transformation	
Shin		Yeshiva University
R01-CA-21365	Cytoplasmic Genes in Normal and Tumorigenic Cells	
Sager		Sidney Farber Cancer Institute

R01-CA-23003	Regulation of Expression of Viral Transformation	
Ozer		Hunter College
R01-CA-24828	Genetic Analysis of Tumorigenesis	
Sager		Sidney Farber Cancer Institute
R01-CA-25342	Complement of Sister Chromatid Exchange to Cell Hybrids	
Siniscalco		Sloan Kettering Institute for Cancer Res.
R01-CA-27607	Coordinated Control of Mammalian Gene Expression	
Lee		University of Southern California
R01-CA-27712	Gene Expression During Mammalian Development	
Croce		Wistar Institute of Anatomy and Biology
R01-CA-27713	Gene Expression During Mammalian Development	
Illmensee		University of Geneva
R01-CA-28559	Study of Malignant Transformation: A Genetic Analysis	
Athwal		College of Medicine and Dentistry of NJ
R01-CA-30938	Structural and Functional Analysis of Cloned MHC Gene	
Weissman		Yale University

INHERITANCE OF NEOPLASMS

R23-CA-28963	Genetic Basis of SJL/J Murine Reticulum Cell Sarcoma	
Bubbers		University of California Los Angeles
R01-CA-29078	Cellular Origins of Rat Hepatic Preneoplasias	
Iannaccone		Northwestern University
R23-CA-29944	Analysis of Genetic Heterogeneity in Fanconi Anemia	
Auerbach		Sloan Kettering Institute for Cancer Res.

PLASMIDS, VIRUSES

R01-CA-11526	Tumor-Inducing Substance of Agrobacterium Tumefaciens	
Kado		University of California Davis
R01-CA-13015	Molecular Basis of Crown Gall Tumorigenesis	
Nester		University of Washington
R01-CA-13015	Molecular Basis of Crown Gall Tumorigenesis	
Nester		University of Washington
R01-CA-14026	Tumor Virus, Plasmid and Cell Analysis	
Goodman		University of California San Francisco

R01-CA-18604 The Mechanism of Tumorigenesis by A. Tumefaciens
Matthysse University of North Carolina Chapel Hill

R01-CA-19402 Molecular Genetics of Agrobacterium Plasmids
Farrand Loyola University Medical Center

R01-CA-26963 Molecular Regulation of Crown-Gall Tumor Growth
Chang University of Wisconsin Parkside

R23-CA-27421 Development of a Eukaryotic Cloning Vehicle
Rogers Oregon State University

R01-CA-27424 Agrobacterium DNA Insertion and Expression in Plants
Goodman University of California San Francisco

R01-CA-28946 Transfection by Endogenous Human Transforming Genes
Cooper Sidney Farber Cancer Institute

R01-CA-29474 Cytology, Biochemistry of Viral-Specific Proteins
Buchanan Massachusetts Institute of Technology

R01-CA-29477 Analysis of Malignancy by Gene Transfer
Kucherlapati Princeton University

IN VIVO AND IN VITRO TUMOR LINES

R01-CA-11683 Coenzymes and Nucleic Acids Metabolism
Kaplan University of California San Diego

R01-CA-24145 Ovarian Tumors in Young Mice
Beamer Jackson Laboratory

R23-CA-24393 Derivation of Nerve Cell Lines from the Brain
Giotta Salk Institute for Biological Studies

R01-CA-24621 Induction-Continuation-Genetics of Experimental Tumor
Morris Howard University

R01-CA-25630 Studies of Malignant Progression Using Human Cells
Smith University of California Berkeley

R01-CA-25718 Swine Melanoma: In Vitro Growth and In Vivo Pathology
Berkelhammer Cancer Research Center

R01-CA-26063 Primary Culture of Prostatic Epithelial Cells
Douglas Tufts University

R01-CA-26110 Androgen-Responsive Prostate Epithelial Cells
McKeehan W. Alton Jones Cell Science Center

R01-CA-28641 Tumor Imaging Using ^{99m}Tc and ^{111}In-Labeled Leukocytes
Dettman Brown University

R01-CA-28668 Biologic Markers for Melanoma
Gehrke University of Missouri Columbia

R01-CA-29440 Biochemical Identification of Organ Specific Melanoma
Mehard University of California San Francisco

R01-CA-29550 Tumor Cell with Varying Degrees of Malignancy
Varani University of Michigan

R01-CA-30082 Genetics and Development of Teratocarcinoma Cells
Nesbitt University of California San Diego

R01-CA-30621 Biological and Immunobiochemical Studies of Human Hemato
Epstein Northwestern University

CONFERENCES

R13-CA-15961 Seminars and Workshops in Techniques of Cancer Research
King University of Colorado Hlth. Sciences Ctr.

R13-CA-28431
Rosenberg Yale University

R13-CA-30001 Cold Spring Harbor Lab Meetings on Cell Proliferation
Watson Cold Spring Harbor Laboratory

R13-CA-30222 International Conference on Prostaglandins and Cancer
Ramwell

R13-CA-30245 1982 Annual Symposium on Fundamental Cancer Research
Lemaistre University of Texas System Cancer Center

R13-CA-31383 Conference on Gene Amplification
Watson Cold Spring Harbor Laboratory

PROGRAM PROJECTS

P01-CA-10893 Cancer Research Center
Busch Baylor College of Medicine

P01-CA-12174 Study of Growth and Cell Control Processes
Green Massachusetts Institute of Technology

P01-CA-12923 A Correlated Study on the Biology of Neoplasia
Baserga Temple University

P01-CA-14294 Tumor Associated Changes of Intestinal and Liver Cells
Isselbacher Massachusetts General Hospital

P01-CA-14454	Membranes in Normal and Cancer Cells	
Racker		Cornell University
P01-CA-15823	Program in Developmental Biology of Cancer	
Pierce		University of Colorado Hlth. Sciences Ctr.
P01-CA-19265	Cancer Biology Research Center	
Ultmann		University of Chicago
P01-CA-20810	Somatic Cell Genetics in Cancer	
Puck		University of Colorado at Boulder
P01-CA-21901	Studies of Normal and Malignant Cell Membranes	
Roseman		Johns Hopkins University
P01-CA-22376	Control of Gene Expression: Normal and Neoplastic	
Feigelson		Columbia University
P01-CA-23052	Program Project on Athymic Mice and Human Tumors	
Kaplan		University of California San Diego
P01-CA-23076	Regulatory Mechanisms in Tumor Biology	
Mueller		University of Wisconsin Madison
P01-CA-25845	Pathobiology of Small Cell Carcinoma of the Lung	
Sorenson		Dartmouth College
P01-CA-25875	Cell Differentiation and Cancer	
Croce		Wistar Institute of Anatomy and Biology
P01-CA-26712	Glycoproteins, the Cytoskeleton and Cancer	
Hynes		Massachusetts Institute of Technology
P01-CA29545	Interferon, Differentiation and Oncogenesis	
Carter		Hahnemann Med. Col. and Hosp. of Philadelphia
P01-CA-29569	Gene Organization and Expression in Eukaryotes	
Watson		Cold Spring Harbor Laboratory

DIFFICULT TO CATEGORIZE

R01-CA-09247	Partial Subsidy for the Journal of Cancer Research	
Philips		American Association for Cancer Research
R01-CA-21607	Secretory Processes in the Prostate Gland	
Smith		University of Massachusetts Medical School
R01-CA-25298	Biology of Human Cutaneous Malignant Melanoma	
Clark		University of Pennsylvania
R01-CA-27120	Interferon System: Action, Induction, and Regulation	
Ts'O		Johns Hopkins University

R01-CA-28571 Erickson	Recognition of Patterns in Cancer-Related Sequences Rockefeller University
R01-CA-29551 Ward	Complement Mediated Tumor Cell Chemotaxis University of Michigan

CONTRACT RESEARCH SUMMARY

Title: Morris Hepatoma Resource Program

Principal Investigator: Dr. Wayne E. Criss
Performing Organization: Howard University College of Medicine
City and State: Washington, DC

Contract Number: NCI-CB-14345-39
Starting Date: 7/1/81 Expiration Date: 6/30/84

Goal: To maintain eleven Morris hepatomas representative of the spectrum of rapidly-to very slow-growing-tumors in stock rats and provide them on request to laboratories for research purposes.

Approach: The hepatomas will be propagated by serial transplantation in rats and periodically monitored by enzyme profiles and assay of specific metabolites to assure stability of each line. Requests for any of the hepatomas will be filled depending on availability by injecting tumor tissue into host rats purchased by the requestor and then shipping them to his/her laboratory by air freight.

Progress: New contract

Significance to Cancer Research: Each of these hepatomas has specific characteristics that make it the tumor of choice for certain research projects. Currently, NCI grants in the areas of enzymology, intermediary metabolism and molecular biology depend upon this liver tumor system.

Project Officer: Dr. Colette Freeman
Program: Tumor Biology Section
FY 81 Funds: $120,000

IMMUNOLOGY PROGRAM

The role of the Immunology Program of the National Cancer Institute is to support studies which contribute to an understanding of the role of the immune system on the development, growth and spread of tumors. The specific areas of investigation supported by the Program include:

1) The synthesis and structure of myeloma proteins in animals and man.

2) The synthesis, structure, and mechanism of action of antibodies capable of reacting with tumor cells and agents which induce tumors.

3) The synthesis, structure and mechanism of action of humoral factors other than antibody which participate in, activate and/or regulate the immune response to tumors. Factors of interest include: complement, interferon, lymphokines, lymphoid cell growth factors, helper factors, suppressor factors as they are involved in immune responses to tumors.

4) The immunobiology of lymphocytes that participate in anti-tumor responses including their development, heterogeneity, interactions and mechanisms of action.

5) The immunobiology of malignancies of the immune system (lymphomas and leukemias) including studies of immunologic markers for the classification and characterization of neoplastic cells and their normal counterparts.

6) The immunobiology of monocytes and macrophages that participate in antitumor responses including their development, heterogeneity, interactions, and mechanisms of action.

7) The identification, isolation and characterization of cell surface determinants which serve as target antigens for the immune response to tumors (e.g., tumor specific antigens, tumor associated antigens).

8) The identification, isolation and characterization of cell surface determinants of lymphocytes and macrophages which are involved in the responses of these cells to tumors.

9) Immune surveillance against the development of tumors of various origins by all immune mechanisms (e.g., T cell immunity, macrophage reactivity, natural killer cell activity).

10) Immunopathology studies on the host-tumor interaction.

11) Immune status of tumor bearing animals and man.

12) Immunogenetic studies relevant to the anti-tumor immune response.

13) Immunobiology of sarcomas, carcinomas, and melanomas.

At one time, the Immunology Program was unique in touching upon all four of the major research thrusts of the Institute -- cause and prevention, detection and diagnosis, treatment and lastly biology. In line with organizational changes within the Institute, the emphasis for the Immunology Program is now centered upon mechanistic studies with responsibility for the more applied immunological efforts in detection and diagnosis residing in the Diagnosis Program and responsibility for explicit treatment studies involving immunologic manipulation residing in the programs of the Division of Cancer Treatment. Reference to the accomplishments in these later areas should be sought in the reports of those programs.

A small number of selected areas are presented to highlight the ongoing research efforts supported by the Immunology Program. The goal is to convey a general sense of the movement in the field. Recognition of all the scientists contributing to progress in Tumor Immunology within the past year would be too extensive to identify in this report. The specific citations used are limited examples of this progress.

A. Molecular Genetics and Biology of Immunoglobulins:

Studies on antigen-binding macromolecules continue to provide important insights into the biology of the immune system which are pertinent to our knowledge of how tumor associated antigens are recognized and how responses to those antigens develop and are regulated.

Three major theories have been proposed to account for the ability of the immune system to react against the tremendous diversity of possible antigens to which we may be exposed. Recent evidence indicates that all three theories may be, at least in part, correct.

An immunoglobulin molecule consists of constant (c) and variable (v) domains in both its light and heavy polypeptide chains. Studies using oligonucleotide probes and the technique of measuring duplex formation due to homology in base sequences have revealed the existence of only one copy of each gene specifying one of the several constant regions per haploid genome. Similar approaches toward mapping the genes which determine the variable domains indicate the existence of large sets of genes existing in closely related clusters (1). Thus, the first mechanisms to account for the existing diversity is the large number of variable region genes which can be combined with any one constant region gene in the synthesis of a specific antibody.

A second mechanism for generating diversity is the rearrangement of genes which occurs at the DNA level as germline cells mature into somatic cells such as the plasmacyte.

Light chains of the immunoglobulin molecule are formed by a rearrangement of genes coding for the variable region (V) with genes encoding for a joining segment (J) and genes encoding for the constant region (Ck or C2). Heavy chains of the immunoglobulin molecule are formed by similar gene rearrangements which include a fourth region (D for Diversity) which is spaced between

V and J. The number of genes coding for the D region is still unknown but there appears to be a small number (perhaps four) J region genes. If, for a heavy chain, any V region gene can combine with any D region gene which can in turn associate with any J region gene, the number of combinations possible by this shuffling provides a second mechanism for generating antibody diversity.

The third process for generating diversity appears to be somatic mutation. Upon sequencing a number of monoclonal antibodies reactive with a defined simple chemical hapten, it was found that IgM antibodies could be grouped into three families based on identity of amino-terminal amino acid sequences. A second class of antibody (IgG) reactive to the same hapten and supposedly sharing the same V regions as the IgM, consistently showed amino acid substitutions not seen in the IgM and which could be explained by a process of somatic mutation occurring after V-D-J region combination (2).

Through these three processes, the immune system maintains a large library of combining sites capable of recognizing the determinants on the surface of any cancer cell regardless of how or where it develops. Already, information from these types of studies is being integrated into efforts to produce antibodies with the most desirable specificities, affinities, subclass type, etc. for application against disease. At the same time, these findings provide important leads to research outside the purview of immunology but significant to the understanding of how other genes are organized and regulated.

B. Natural Cell Mediated Immunity:

Natural cell mediated immunity is an immune effector mechanism unique from the standpoint that it represents a cytotoxic capability which exists at a high level without previous exposure (i.e. priming) to the target cell. In contrast, responses of bursal equivalent-derived (B) lymphocytes and thymus-dependent (T) lymphocytes are generally minimal until after exposure to antigen. The role of natural cell mediated immunity against tumors is a particularly active research area.

The cells mediating this type of immunity appear to be rather heterogeneous. For example, in mice one type is called the natural killer (NK) cell and a second type is referred to as NC (for natural cell-mediated cytotoxicity) distinguishable from NK cells by the type of target cells it is capable of lysing, its activity in various mouse strains and other features (3). A third type resembling NK in most features but reacting against sarcomas and other solid tumors rather than lymphomas is designated NKs. (4). Evidence on the presence of cell surface markers indicates that NK cells share some common determinants with lymphocytes of the T lineage (5) but the NC cell lacks these markers (6) and there is no consensus as to the origin of all the various cells which mediate natural cytotoxicity. A feature that is characteristic of cells mediating natural cytotoxicity as opposed to other forms of cell mediated immunity (such as cytotoxic T cells and antibody-dependent cytotoxicity by K cells) is their broad target specificity. While NK cells are capable of lysing a variety of seemingly unrelated tumors, T cell

cytotoxicity and ADCC are specific for either a single tumor or tumors which are cross reactive. The broad specificity of NK cells is evident in cloned cell lines (7) and thus does not represent the participation of a heterogeneous population of cells of different specificities.

The functional properties of NK cells have led to speculation that they play a surveillance role in preventing the outgrowth of transformed cells. One line of evidence supporting this notion develops from study of the mutant "beige" mouse. This animal has very low levels of natural killer activity and it has been reported that these deficient animals support more rapid growth of transplanted lymphoid tumors than do normal controls (8), thus inferring a role of NK cells in limiting tumor outgrowth. A second approach to this question has demonstrated that variants of cell lines selected for their ability to produce tumors in mouse strains with either high or low levels of natural cell mediated immunity are respectively resistant or sensitive to lysis by NK cells. Again this is consistent with an in vivo surveillance role by NK cells.

Although natural cell mediated immunity exists without prior immunization, the level of activity can be modulated. Interferon and substances which induce interferon have been shown to be capable of augmenting NK activity. In most cases this is demonstrated by a simple increase in killing at various effector:target ratios after pretreatment with interferon (9,10,11). The mechanism by which this increase occurs appears complex. First, it may involve the maturation of pre-NK cells to NK as measured by both the induction of cell surface markers such as LyT-5 and Nk-1 and the ability to become cytotoxic (12,13). Secondly, the rate of killing is increased indicating a more efficient cytotoxicity function (13). Other soluble mediators can also regulate NK activity, i.e., interleukin-2 or T cell growth factor (14). Cellular mechanisms of supression of natural immunity also appear to be operative (15).

The discovery and study of natural cell-mediated immunity has a number of ramifications. First, it provides information on a new effector mechanism potentially important in anti-tumor immunity. Secondly, this information clears up many questions which had arisen in comparing immune responses between normal controls and immunized subjects (e.g., the source of high "spontaneous" tumor cell killing). Third, the modulation of this activity by mediators such as interferon helps explain some of the manifold effects of this substance and provides some rational base for therapy. Fourth, the broad specificity of natural killer cells may make them very useful in adoptive immunotherapy. Underlying this and many other facets of tumor immunology is a growing awareness of the complex interactions of the immune system as a whole. Because there exists so many regulated interactions, biological modulation is likely to pose an extremely complex problem.

C. Monoclonal Antibodies:

The application of somatic cell hybridization to the fusion of a lymphocyte with a myeloma cell to produce a hybridoma has provided a major advance

in cancer immunology. Hybridomas produce monoclonal antibody molecules which, by their very nature, are uniform with respect to binding specificity. Mixtures of antigens unseparable by conventional heterologous antisera are easily resolved into individual components by analysis with monoclonal antibodies. This provides a new opportunity to dissect the cell surface composition of both lymphocytes and the tumor cells they react with.

For example, Schlossman and colleagues (16,17) have prepared and characterized a series of monoclonal antibodies useful in defining normal human T lymphocyte subclasses and their transformed counterparts. Cell surface antigens designated T9 and T10 are found on early thymocytes and most T-cell acute lymphatic leukemias appear to be the transformed counterparts of these early cells. Cortical thymocytes bear surface antigens T10, T6, T4 and T5 and some T cell-acute lymphatic leukemias and most T cell lymphoblastic lymphomas are the transformed counterparts of this stage. The more mature medullary thymocyte bears the T10, T1, T3 and T4 or T5 cell surface antigens and transformed counterparts here include a small number of T-cell lymphoblastic lymphomas and rare T-cell acute lymphatic leukemias. Peripheral T cells bearing the T1, T3 and T4 antigens represent the subpopulation normally involved in the induction of immune responses. Most T-cell chronic lymphatic leukemias, cells of the Sézary syndrome and cells of Mycosis fungiodes also fall in this category. The normal T cell subpopulation capable of suppressing immune responses or of exhibiting direct cytotoxicity bear the T1, T3 and T5 cell surface antigens as do the cells in rare cases of T-cell chronic lymphatic leukemia.

These studies not only shed light on the processes of normal T cell development and function but also provide a subclassification of lymphomas and leukemias which may prove useful in diagnosis and in deciding most effective treatment. Similar approaches by other laboratories including those of Hansen, Levy, Kersey, Springer, Russell and Kaplan are providing additional information on cell surface markers for T cells and extend the technique to B cells and the monocyte/macrophage.

Human melanoma is an example of a tumor which is being extensively studied from the standpoint of preparing monoclonal antibodies with high relative specificities for the tumor which can then be used for studies in biology, pathology, diagnosis and potentially even therapy.

There appears to be several major categories of melanoma associated antigens. The first is a large glycoprotein of approximately 240,000 daltons described by Reisfeld, Ferrone, and colleagues (18). A second smaller glycoprotein (M.W. of 95,000-97,000) has been described by the Hellstroms and their colleagues. In addition, this laboratory has developed two very sensitive assays for quantitating this antigen on the cell surface which should be widely applicable (19). The importance of this kind of technical development is that it opens the possibility of diagnostic application when there is a quantitative rather than qualitative antigenic difference between normal and tumor cells. A third type of glycoprotein antigen which has been described is of even lower molecular weight (25,000-40,000) but it seems likely that this type represents subunits of larger glycoproteins which are in turn relatively specific for melanoma cells and/or is a component of

histocompatability antigens which are found on melanoma as well as other cells (20). A fourth type of melanoma associated antigen which has been described by Lloyd, Old and colleagues is a glycolipid (21) which is either identical or very similar to the GD3 ganglioside previously shown to exist at very low levels in the brain and pigmented areas of the eye. This finding is of interest in that it focuses attention on a class of biological molecules which have not been well studied in terms of tumor antigenicity. Also, it demonstrates the applicability of monoclonal antibodies in analyses of non-protein antigens. In light of the finding by Steplewski and co-workers that an antigen quite specific for human colon carcinoma is also a glycolipid, it is likely that considerable future attention will be devoted to serological analysis of this class of cell surface component.

The NCI Immunology Program sponsored a workshop on Monoclonal Antibodies to Human Melanoma Antigens in March of 1981 to facilitate an exchange of information among the major laboratories involved in this area of research. This proved to be a useful format in comparing data from the different groups, discussing technical details in depth and arranging for an exchange of antibodies among the participant laboratories.

From this exchange and comparison, it should be possible to define those antibodies most worthy of application in diagnosis and therapy. It is, however, equally important to continue the basic studies relating to cell-surface antigens on tumor cells. For example, we have yet to learn whether tumor-specific antigens exist on human tumors. If the antigens are only tumor-associated (i.e., also found on other tumors or normal cells at some stage of development), what is their cellular function and why are they in higher concentration on transformed cells? Also, the ability to work with a defined antigen will greatly simplify the task of studying the induction and regulation of the immune response against tumor cells. Further, studies on the clonality of tumors and on the problem of recurrence versus new tumor development should be greatly facilitated by reference to appropriately defined cell surface antigens.

In an effort to promote the shared use of hybridomas and monoclonal antibodies, the NCI Immunology Program has supported a Cell Bank and Distribution Center which makes a wide variety of cell lines in this and other categories available to interested investigators (CB 23886).

D. Immune Response Genes:

Baruj Benacerraf, a grantee in the NCI Immunology Program for the past eight years, was awarded the 1980 Nobel Prize in Physiology and Medicine, along with George Snell and Jean Dausset. Dr. Benacerraf's specific accomplishments relate to his studies on the role of the major histocompatability complex in immune regulation (24). His most recent work continues in this area and includes studies on soluble factors bearing antigens determined by genes in the Ir region of the major histocompatibility complex. These same factors also have regions which are antigenically cross reactive with the antigen binding portion of immunoglobulin molecules. These factors are

involved in the collaborations which must occur among macrophages, B cells and T cells for some types of immune response to occur.

The future study of these interactions and the genes which govern them will be important to our understanding of the functioning of the immune system.

E. Meeting Support:

The following meetings, conferences and workshops were supported by the NCI Immunology Program during fiscal year 1981:

"Mechanisms in Human Cancer Immunology Symposium" - Galveston, Texas
October 1980

"Host Defense in Neoplasia" - Plymouth, New Hampshire
July 1981

"Mechanisms in Cell Mediated Cytotoxicity" - Carry-Le-Rouet, France
September, 1981

"1981 Midwest Immunology Conference" - Minneapolis, Minnesota
October 1981

"International Cancer Congress" - Seattle, Washington
1982

FISCAL YEAR 1981

IMMUNOLOGY PROGRAM

SUMMARY OF GRANTS BY SUBCATEGORY

(Includes P01, R01, R23, R13 Grants)

(Dollars in Thousands)

Subcategory	No. of Grants	Total Costs Awarded
Myeloma Proteins	20	$ 2,612
Cell Surface Antigens	66	8,086
Cell Surface Determinants of Lymphocytes & Macrophages	40	4,207
Humoral Factors other than Antibody	36	3,369
Tumor-Related Antibodies	17	1,865
Immunobiology of Sarcomas, Carcinomas & Melanomas	10	843
Host/Tumor Immunopathology	22	2,422
Effects of Disease on Immune Function	51	5,732
Immunotherapy: Mechanisms Rather Than Therapeutic Result	8	976
Lymphocytes	94	15,326
Monocytes and Macrophages	28	3,572
Malignancies of the Immune System (Lymphoma/Leukemia)	33	3,476
Immune Surveillance	32	3,131
Immunotherapy in Animal Models	6	698
Bone Marrow Transplantation	7	895
	470	$57,211

References

1. Cory, S. and Adams, J.M., 1980. "Deletions Are Associated with Somatic Rearrangement of Immunoglobulin Heavy Genes," Cell, 19:37-51, (CA 12421)

2. Gearhart, P.J., Johnson, N.D., Douglas, R . and Hood, L., 1981. "IgG Antibodies to Phosphorylcholine Exhibit More Diversity Than Their IgM Counterparts," Nature, 291:29-34, (CA 25507)

3. Stutman, O. and Cuttito, M.J., 1981. "Normal Levels of Natural Cytotoxic Cells Against Solid Tumors in NK-Deficient Beige Mice," Nature, 290:254-257, (CA 15988)

4. Burton, R.C., 1980. "Alloantisera Selectively Reactive with NK Cells: Characterization and Use in Defining NK Cell Classes", In: Herberman, R.B., (ed.), Natural Cell-Mediated Immunity Against Tumors, Academic Press, New York, (CA 17800)

5. Koo, G.C., Jacobson, J.B., Hammerling, G.J. and Hammerling, U., 1980. "Antigenic Profile of Murine Natural Killer Cells," J. Immunol., 125: 1003-1006, (CA 25416)

6. Lattime, E.C., Pecoraro, G.A. and Stutman, O., 1981. "Natural Cytotoxic Cells Against Solid Tumors in Mice," III. "A Comparison of Effector Cell Antigenic Phenotype and Target Cell Recognition Structures with Those of NK Cells," J. Immunol., 126:2011-2014, (CA 17818)

7. Dennert, G., Yogeeswaran, G. and Yamagata, S., 1981. "Cloned Cell Lines with Natural Killer Activity - Specificity, Function and Cell Markers," J. Exp. Med., 153:545-556, (CA 15581).

8. Karre, K., Klein, G.O., Kiessling, R., Klein, G. and Roder, J.C., 1980. "Low Natural In Vivo Resistance to Syngeneic Leukemias in Natural Killer-Deficient Mice," Nature, 284:624-626, (CA 26782)

9. Orn, A., Gidlund, M., Ojo, E., Gronvik, K., Andersson, J., Wigzell, H., Murgita, R.A., Sennik, A. and Gresser, I., 1980. "Factors Controlling the Augmentation of Natural Killer Cells," In: Herberman, R.B. (ed.), Natural Cell-Mediated Immunity Against Tumors, Academic Press, New York, (CB 64033)

10. Trinchieri, G., Perussia, B. and Santoli,D., 1980. "Spontaneous Cell Mediated Cytotoxicity: Modulation by Interferon," In: Herberman, R.B. (ed.), Natural Cell Mediated Immunity Against Tumors, Academic Press, New York, (CA 20833)

11. Zarling, J.M., 1980. "Augmentation of Human Natural Killer Cell Activity by Purified Interferon and Polyribonucleotides," In: Herberman, R.B. (ed.), Natural Cell Mediated Immunity Against Tumors, Academic Press, New York, (CA 26738)

12. Minato, N., Ried, L., Cantor, H., Lengyel, P. and Bloom, B.R., 1980. "Mode of Regulation of Natural Killer Cell Activity by Interferon," J. Exp. Med., 152:124-137, (CB 74147)

13. Silva, A., Bonavida, B. and Targan, S., 1980. "Mode of Action of Interferon-Mediated Modulation of Natural Killer Cytotoxic Activity: Recruitment of Pre-NK Cells and Enhanced Kinetics of Lysis," J. Immunol., 125:479-484, (CA 12800)

14. Henney, C.S., Kuribayashi, K., Kern, D.E. and Gillis, S., 1981. "Interleukin-2 Augments Natural Killer Cell Activity: Natural Killer Cell Activity," Nature, 291:335-338, (CA 24537)

15. Lotzova, E., 1980. "C. parvum-Mediated Suppression of the Phenomenon of Natural Killing and Its Analysis," In: Herberman, R. (ed.) Natural Cell-Mediated Immunity Against Tumors, Academic Press, New York, (CA 24537)

16. Reinberg, E.L., Kung, P.C., Goldstein, G., Levey, R.H. and Schlossman, S.F., 1980. "Discrete Stages of Human Intrathymic Differentiation: Analysis of Normal Thymocytes and Leukemic Lymphoblasts of T lineage," Proc. Nat'l. Acad. Sci. (U.S.), 77:1588-1592, (CA 25369)

17. Schlossman, S., 1981. "Anti-Human T Cell Hybridomas," Workshop on Hybridomas in the Diagnosis and Treatment of Cancer. In press. (CA 25369)

18. Galloway, D.R., Imai, K., Ferrone, S. and Reisfeld, R.A., 1981. "Molecular Profiles of Human Melanoma Associated Antigens," Fed. Proc., 40: 231-236, (CA 28420)

19. Brown, J.P., Woodbury, R.G., Hart, C.E., Hellstrom, I. and Hellstrom, K.E., 1981. "Quantitative Analysis of Melanoma-Associated Antigen p. 97 in Normal and Neoplastic Tissues," Proc. Nat'l. Acad. Sci. (U.S.), 78:539-543 (CA 19149)

20. Mitchell, K.F., Fuhrer, J.P., Steplewski, Z. and Koprowski, H., 1980. "Biochemical Characterization of Human Melanoma Cell Surfaces: Dissection with Monoclonal Antibodies," Proc. Nat'l Acad. Sci. (U.S.), 77:7287-7291, (CA 25874)

21. Dippold, W.G., Lloyd, K.O., Li, L.T.C., Ikeda, H., Oettgen, H.F. and Old, L.J., 1980. "Cell Surface Antigens of Human Malignant Melanoma: Definition of Six Antigenic Systems with Mouse Monoclonal Antibodies," Proc. Nat'l. Acad. Sci. (U.S.), 77:6114-6118, (CA 21445)

22. Olsson, L. and Kaplan, H.S., 1980. "Human-Human Hybridomas Producing Monoclonal Antibodies of Predefined Antigenic Specificity," Proc. Nat'l. Acad. Sci. (U.S.), 77:5429-5431, (now supported by CA 29876)

23. Croce, C.M., Linnenback, A., Hall, W., Steplewski, Z. and Koprowski, H., 1980. "Production of Human Hybridomas Secreting Antibodies to Measles Virus," Nature, 288:488-489, (CA 23568)

24. Benacerraf, B., 1981. "Role of MHC Gene Products in Immune Regulation," Science, 212:1229-1238, (CA 14723)

R01-CA-04946 Hidden Immunoglobulin Allotypes in Mice
Bosma Institute for Cancer Research

R01-CA-08497 Abnormal Proteins in Multiple Myeloma
Putnam Indiana University Bloomington

R01-CA-10056 Proteins in Multiple Myeloma and Related Blood Diseases
Solomon University of Tennessee Knoxville

R01-CA-12421 Structure of Immunoglobulin Messenger RNAs and Genes
Adams Walter and ELiza Hall Inst. Medical Res.

R01-CA-13014 Proteins of Plasma Cell Cancers
Beychok Columbia University

R01-CA-13953 Control of Myeloma Tumor Growth
Huang Johns Hopkins University

R01-CA-16858 Genetics and Biochemistry of Myeloma Ig Production
Morrison Columbia University

R01-CA-19616 Immunoglobulins in Multiple Myeloma and Amyloidosis
Edmundson University of Utah

R01-CA-20088 Tumor-Bound Ig--An Expression of Antitumor Immunity
Witz Tel Aviv University

R01-CA-22105 Allotypes of Murine Immunoglobulins
Warner University of New Mexico Albuquerque

R01-CA-23885 Secretory Immunoglobulin Studies
Lamm New York University

R01-CA-24432 Sequence, Shape and Specificity of Antibodies
Haber Massachusetts General Hospital

R01-CA-25049 Structure and Genetics of Antibody Variable Regions
Cannon Brandeis University

R01-CA-25166 Defects in Immunoglobulin Production in Mouse Myeloma
Levine State University of New York Stony Brook

P01-CA-25319 Synthesis of Human Myeloma Variable Domains in E. coli
Beychok Columbia University

R01-CA-25507 B Cell Expression of Immunoglobulin V and C Regions
Gearhart Carnegie Institution of Washington, DC

R01-CA-25754 Control of Immunoglobulin Synthesis
Storb University of Washington

R01-CA-28871 Ig Processing by Lymphocyte Endoplasmic Reticulum
Green St. Louis University

R01-CA-29634 Immunoglobulin mRNA and Genes in T Cell Tumors
Kemp Walter and Eliza Hall Inst. Medical Res.

R01-CA-29679 Genetic Analysis of Membrane Immunoglobulin
Sibley University of Washington

R01-CA-31013 Immunoglobulin Genes of Normal and Leukemic Human DNA
Blattner University of Wisconsin Madison

CELL SURFACE ANTIGENS

R01-CA-12851 Embryonic and Virally Induced Tumor-Cell Membrane Antigens
Sanders University of Texas Austin

R01-CA-13070 Immunity to Human Cancer--Functional Components
Dawson Duke University

R01-CA-13287 Genetic Basis of Antigenic Variation
Hyman Salk Institute for Biological Studies

R01-CA-13844 Isolation of Tumor Antigens of Human Melanoma
Bystryn New York University

R01-CA-14054 Malignant Behavior and Cellular Antigen Expression
Klein Caroline Institute

R01-CA-16069 Immunochemical Characterization of Antigens in Melanoma
Ferrone Scripps Clinic and Research Foundation

R01-CA-17533 Myelogenous Leukemia-Associated Antigens
Wust University of Tennessee Knoxville

R01-CA-18470 Antigenicity and Tumorigenicity of Somatic Cell Hybrids
Knowles Wistar Institute of Anatomy and Biology

R01-CA-18600 Masking of Antigens at Cancer Cell Surfaces
Codington Massachusetts General Hospital

R01-CA-18609 Biological Role of Alloantigens
Acton University of Alabama in Birmingham

R01-CA-19149 Transplantation Antigenicity of Virus Induced Tumors
Hellstrom Fred Hutchinson Cancer Research Center

R01-CA-19224 Relation of Blood Group and Human Tumor Antigens
Hakomori Fred Hutchinson Cancer Research Center

R01-CA-19304 Human Leukemia and Lymphoma Associated Antigens
Seon Roswell Park Memorial Institute

P01-CA-19765	Human Cancer Serology	
Old		Sloan Kettering Institute for Cancer Res.
R01-CA-20168	Neoplastic and Normal Cell Thymus-Leukemia Antigens	
Little		Jewish Hospital of St. Louis
R01-CA-21223	Antitumor Antibodies Generated In Vitro	
Levy		Stanford University
R01-CA-21279	Isolation and Characterization of Fc Receptors	
Cooper		
R01-CA-21445	Antigens of Human Malignant Melanoma	
Lloyd		Sloan Kettering Institute for Cancer Res.
P01-CA-22507	Immunogenetics of the Major Histocompatibility Complex	
Dupont		Sloan Kettering Institute for Cancer Res.
R01-CA-22540	Human Cancer Relation of MN and Precursor Structures	
Springer		Evanston Hospital
R01-CA-22674	Characterization of Fetal Antigens in Tumors	
Coggin		University of South Alabama
R01-CA-22794	Human Neuroblastoma Cell Surface Antigens	
Seeger		University of California Los Angeles
P01-CA-23115	New Immunologic Approaches to Lymphoid Neoplasms	
Frenkel		University of Texas Hlth. Sci. Ctr. Dallas
R01-CA-23404	Serologic Screening for Contagion of Human Sarcomas	
Hirshaut		Sloan Kettering Institute for Cancer Res.
R01-CA-23568	Immunoresponse to Human Surface Antigens	
Croce		Wistar Institute of Anatomy and Biology
R01-CA-24024	In Vitro Generation of Immunity to Human Colon Cancer	
Tom		University of Texas Hlth. Sci. Ctr. Houston
R01-CA-24910	Oncofetal Antigens in Embryogenesis and Tumor Growth	
Rosenberg		University of Maryland Balt. Co. Campus
R01-CA-25139	Study of Group 5 Antigens in Hematologic Malignancies	
Warren		Fred Hutchinson Cancer Research Center
R01-CA-25154	Tumor-Specific Immunity and Histocompatibility Complex	
Chauvenet		University of Texas Hlth. Sci. Ctr. San Antonio
R01-CA-25171	Cell Surface Antigens of Murine Tumors	
Callahan		Scripps Clinic and Research Foundation
R01-CA-25558	Cell Surface Antigens of Chemically Induced Sarcomas	
Hellstrom		Fred Hutchinson Cancer Research Center

R01-CA-25852	Isolation and Characterization of Heterophile Antigens	
Merrick		State University of New York at Buffalo
P01-CA-25874	Human Melanoma and Tumor Specific Monoclonal Antibodies	
Koprowski		Wistar Institute of Anatomy and Biology
R01-CA-25910	Production of Antibodies to Tumor Associated Antigens	
Leung		Rutgers, The State University New Brunswick
R01-CA-26184	Antigens of Human Ovarian Tumors	
Lloyd		Sloan Kettering Institute for Cancer Res.
R01-CA-26321	Cell-Surface Antigens of Murine Tumors	
Allison		University of Texas System Cancer Center
R01-CA-26456	Cell Surface Antigens in Murine Leukemia	
Callahan		Scripps Clinic and Research Foundation
R01-CA-26479	Immune Functions of Tumor Cell Variants	
Fuji		Roswell Park Memorial Institute
R23-CA-26584	The Molecular Nature of Tumor Antigens	
Woodbury		Fred Hutchinson Cancer Research Center
R01-CA-26891	Surface Antigens of Rat Hepatocellular Carcinomas	
Allison		University of Texas System Cancer Center
R01-CA-27124	Molecular Approaches to Human Colon Cancer	
Kahan		University of Texas Hlth. Sci. Ctr. Houston
R01-CA-27471	Modulation of Cellular Responses by Membrane Fluidity	
Shinitzky		Weizmann Institute of Science
R01-CA-27534	Nucleolar Antigens of Human Cancer Cells	
Busch		Baylor College of Medicine
R01-CA-27628	Tumor-Specific and Tumor-Associated Antigens	
Milgrom		State University of New York at Buffalo
R01-CA-27841	Antigens of Chemically Transformed Mouse Fibroblasts	
Brown		Fred Hutchinson Cancer Research Center
P01-CA-28166	Molecular Immunology and Pathobiology of Neoplasia	
Edgington		Scripps Clinic and Research Foundation
R01-CA-28212	Antisera for Human Tumor-Associated Antigens	
Minden		National Jewish Hospital & Research Ctr.
R01-CA-28230	Swine Melanoma Antigens: Isolation and Evaluation	
Hook		University of Missouri Columbia
R01-CA-28253	Immune Response to Syngeneic Leukemic B Cell Antigens	
Ricardo		University of Tenn. Center Health Scien.

R01-CA-28420 Molecular Profile of Human Melanoma Antigens
Reisfeld Scripps Clinic and Research Foundation

R01-CA-28448 Forssman Antigen/Antibody and Human Adenocarcinoma
Levine Sloan Kettering Institute for Cancer Res.

R01-CA-28461 Cell Surface Antigens of Mouse Sarcomas
De Leo Sloan Kettering Institute for Cancer Res.

R23-CA-28526 Analysis of Human Leukemia Cells with Hybridomas
Le Bien University of Minnesota of Minneapolis-St. Paul

R01-CA-28564 Human Squamous Cell Carcinoma: Culture and Serology
Carey University of Michigan

R01-CA-28564 Human Squamous Cell Carcinoma: Culture and Serology
Carey University of Michigan

R01-CA-28619 Purification of Human Sarcoma Heterophile Antigens
Hirshaut Sloan Kettering Institute for Cancer Res.

R01-CA-28732 Studies of Immune Complexes in Patients with Leukemia
Williams University of New Mexico Albuquerque

R01-CA-28775 Cross-Reacting Antigens on Spermatozoa and Tumors
Anderson Medical Research Foundation of Oregon

R01-CA-29216 Characterization of a Tumor Antigen on Leukemia Cells
Garver Medical College of Georgia

R01-CA-29516 Human Antibodies to Melanoma
Wright Pacific Northwest Research Foundation

R01-CA-29534 Oral Immunopathology: Oral Squamous Cell Carcinoma
Eskinazi University of Southern California

R23-CA-29539 Role of Glycolipids in Immune Cell Function
Young University of Virginia

R01-CA-29662 Complex Carbohydrate Chemistry in Leukocytes
Klock University of California San Francisco

R01-CA-29863 Immunochemical Genetics of Murine Alloantigens
Michaelson New York University

R01-CA-29886 Tumor-Host Associated Immunological Specificities
De Witt University of Utah

R01-CA-29897 Antigenic Profile of Human Leukemic Cells
Pellegrino Scripps Clinic and Research Foundation

R01-CA-29989 HLA Alloantigens on Cultured Human Tumor Cell Lines
Pollack Sloan Kettering Institute for Cancer Res.

R01-CA-30209 Immunochemical Studies of Gastrointestinal Cancer
Alpert Baylor College of Medicine

R01-CA-30266 Membrane Antigen Organization in Tumor Immunity
Gooding Emory University

R01-CA-30501 Isolation and Characterization of the Common ALL Antigen
Mills City of Hope National Medical Center

R01-CA-30561 Tumor Associated Antigens of UV-Induced Tumors
Spellman University of New Mexico Albuquerque

CELL SURFACE DETERMINANTS OF LYMPHOCYTES AND MACROPHAGES

R01-CA-04681 Genetic Studies with Mammalian Cells
Herzenberg Stanford University

R01-CA-10097 Cellular Antigens of Normal and Malignant Rat Tissues
Wettstein Wistar Institute of Anatomy and Biology

R01-CA-14061 Chicken Lymphocyte Alloantigens and Viral Oncogenesis
Gilmour New York University

R01-CA-15146 Genetic Control of the Immune Response
Gasser University of Pennsylvania

R01-CA-15318 Neutrophil Antigens; Pathophysiology and Chemistry
Lalezari Montefiore Hospital and Medical Center

R01-CA-16071 Urine as Source of Human Cell Surface Markers
Pellegrino Scripps Clinic and Research Foundation

R01-CA-17680 Genetics, the Lymphocyte and Tumor Regression
Collins University of New Hampshire

R01-CA-18640 Behavior of Weak Transplantation Antigens
Silvers University of Pennsylvania

R01-CA-18659 Chemical Genetic and Cellular Aspects of Immunogenicity
Gill University of Pittsburgh

R01-CA-18734 Immunologic Studies Related to Malignancy
Jones University of Colorado Hlth. Sciences Ctr.

R01-CA-20107 B Cell Alloantigens, Molecular Basis and Disease Aspects
Winchester Rockefeller University

R01-CA-20473 Immunogenetics of the TLA Region of Chromosome 17
Boyse Sloan Kettering Institute for Cancer Res.

R01-CA-20500	Structural and Serological Studies on Ia Antigens	
Cullen		Washington University
R01-CA-20531	Genetic Analysis of Normal and Malignant Lymphocytes	
Yunis		Sidney Farber Cancer Institute
R01-CA-20820	Structural Studies of the Products of the H-2 Complex	
Freed		Johns Hopkins University
P01-CA-21112	Dyscrasias of Plasma Cells and Macrophages	
Osserman		Columbia University
R01-CA-21651	Teratocarcinoma and Embryonal Tumors: Surface Antigens	
ArtzT		Sloan Kettering Institute for Cancer Res.
R01-CA-22080	Cell Surface Antigens of Lymphocytes and Tumor Cells	
McKenzie		University of Melbourne
R01-CA-22131	Immunogenetics of Ly Systems	
Boyse		Sloan Kettering Institute for Cancer Res.
R01-CA-22662	Genetics and Function of Murine Ia Antigens	
Frelinger		University of Southern California
R01-CA-23026	The Major Histocompatibility Complex of the Rabbit	
Tissot		University of Illinois Medical Center
R01-CA-23027	Immunogenetic Mapping of the Cell Surface	
Flaherty		New York State Department of Health
R01-CA-23030	Structure Studies of Ia Alloantigens	
Silver		Scripps Clinic and Research Foundation
R01-CA-23469	Cells Involved in Spontaneous Regression of Tumors	
Yang		University of Connecticut Storrs
R01-CA-23677	New Method for Separating Leucocyte Subpopulations	
Parker		University of Southern California
R01-CA-24433	Structures of Histocompatibility-2 Membrane Antigens	
Sears		University of California Santa Barbara
R01-CA-24437	Expression of T Lymphocyte Differentiation Antigens	
Esselman		Michigan State University
R01-CA-24473	Genetics and Functions of (H-2 Linked) I Region	
David		Mayo Foundation
R01-CA-25038	Major Histocompatibility Complex in the Wild Rat	
Cramer		University of Pittsburgh
R01-CA-25041	Murine T Lymphocyte Receptors for Alloantigens	
Neefe		Georgetown University

R01-CA-25044	Surface IgM of Malignant Lymphocytes and Plasma Cells	
Hickman		Jewish Hospital of St. Louis
R01-CA-25893	Cell Surface Molecules: Hematopoietic Differentiation	
Hyman		Salk Institute for Biological Studies
R01-CA-26297	Primary Structure of MHC I Region Associated Antigens	
McKean		Mayo Foundation
R01-CA-27063	Genetics of Cytotoxicity to Virus Modification in Man	
Dubey		Sidney Farber Cancer Institute
R01-CA-27547	Chemistry of Tumoricidal Macrophage Surface Antigens	
Springer		Harvard University
R01-CA-27824	Tumor Membrane Composition and Immune Function	
Whisnant		Duke University
R01-CA-27955	Role of the H-2K Gene in Hybrid Resistance	
Williams		Northwestern University
R23-CA-28271	Character of B Lymphocyte Differentiation Antigens	
Ades		Medical University of South Carolina
R01-CA-28992	Membrane Lectins on Normal and Neoplastic Lymphocytes	
Decker		Medical University of South Carolina
R01-CA-29111	Expression of H-2 Antigens on SJL/J Tumors	
Beisel		Wayne State University
R01-CA-29194	Somatic Cell Genetics of Cell Surface Antigens	
Rajan		Yeshiva University
R01-CA-29548	Differentiation Antigens on Human Lymphocytes	
Hansen		Pacific Northwest Research Foundation
R01-CA-29657	Genetic Control in Leukemogenesis	
Haran-Ghera		Weizmann Institute of Science
R23-CA-29738	Macrophage Membrane and Immunomodulators	
Mitchell		University of Southern California
R01-CA-29979	Immunogenetics of Self-Identification	
Yamazaki		Monell Chemical Senses Center
R01-CA-30654	Regulation of Immune Responses by Fc Portion of Antibody	
Morgan		Scripps Clinic and Research Foundation
R01-CA-31799	Chemistry of Tumoricidal Macrophage Surface Antigens	
Springer		Sidney Farber Cancer Institute

R01-CA-01786	Human Blood and Tissue Proteins	
Deutsch		University of Wisconsin Madison
R01-CA-07191	T Lymphocytes and Lymphotoxin in Tumor Immunity	
Rosenau		University of California San Francisco
R01-CA-15129	A Serum Immunosuppressive Factor in Cancer	
Moolten		Boston University
R01-CA-17643	Regulation of T-Cell Proliferation and Differentiation	
Smith		Dartmouth College
R01-CA-18893	Killing of Cancer Cells by BCG Activated Cells	
Warfel		Sloan Kettering Institute for Cancer Res.
R01-CA-19148	Lymphocyte Allogeneic Inhibition and Tumor Immunity	
Hellstrom		Fred Hutchinson Cancer Research Center
R01-CA-19529	Cell-Mediated Immunity in Humans: Mechanisms and Uses	
Valentine		New York University
R01-CA-19721	Human Interferon Production for Antitumor Studies	
Tan		University of Calgary
R01-CA-20819	Phagocytic Cells: Regulation, Dysfunction and Disease	
Van Epps		University of New Mexico
R01-CA-23681	Factors Affecting Phagocyte Responses to Lipids	
Turner		Duke University
R01-CA-24441	Biochemical Studies of Lymphokines and Related Agents	
Mayer		Johns Hopkins University
R01-CA-24447	Complement Attack Proteins as Lymphocyte Surface AGS	
Kolb		University of Texas San Antonio
R01-CA-24476	T-Lymphocyte Differentiation	
Incefy		Sloan Kettering Institute for Cancer Res.
R01-CA-24916	Studies of a Tumor Factor That Affects Macrophages	
Sundharadas		University of Wisconsin Madison
R01-CA-24974	Chemical and Immunological Characteristics of Thymosin	
Goldstein		George Washington University
R01-CA-25388	Complement and Immune Complexes in Lymphosarcoma	
Day		Sloan Kettering Institute for Cancer Res.
R01-CA-25750	Structure-Function Relations of Immunoregulatory Protein	
Miller		University of Chicago

R01-CA-25756 Regulation of Cell Growth by 5'-Methylthioadenosine
Ferro Oregon State University

R01-CA-25943 Immunobiochemistry of Macrophage-Derived Factors
Elgert Virginia Polytechnic Inst. and St. Univ.

R01-CA-26019 Isolation of Macrophage Agglutination Factor
Godfrey State University of New York Stony Brook

R01-CA-26051 Lymphokines Formed In Vivo: Role in Tumor Suppression
Moulton University of Texas Med. Br. Galveston

R01-CA-26143 Control of Complement-Mediated Tumor Cell Cytolysis
Lint Rush-Presbyterian-St. Luke's Medical Ctr.

R01-CA-26462 Role of Macrophage Arginase in Tumor Immunity
Reiss University of Colorado Hlth. Sciences Ctr.

R01-CA-26504 Regulation of Granulocyte and Macrophage Production
Stanley Yeshiva University

R01-CA-26842 Biological Functions of Alpha 2 Macroglobulin
Stein-Streilein University of Texas Hlth. Sci. Ctr. Dallas

R01-CA-27452 Complement Membrane Attack Proteins Binding and Biosynthesis
Sundsmo Trudeau Institute

R23-CA-27565 Tumor Cell Killing by a Soluble Macrophage Product
Sharma Palo Alto Medical Research Foundation

R01-CA-27629 Tumor Immune RNA: A Biochemical Characterization
Paque University of Texas Hlth. Sci. Ctr. San Antonio

R01-CA-27701 Human Immunoregulatory Gangliosides
Ladisch University of California Los Angeles

R01-CA-27903 Interferon as a Mediator of Cellular Immunity
Epstein University of California San Francisco

R01-CA-28123 The Induction of Human Interferon in C-10 Cells
Huang Johns Hopkins University

R01-CA-28419 Control of Normal and Leukemic T-Cell Proliferation
Gillis Fred Hutchinson Cancer Research Center

R01-CA-28471 Biology of Solid Tumor Growth and Immune Rejection
Dvorak Beth Israel Hospital

R23-CA-29828 Lymphokine-Directed Monocyte-Macrophage Cytotoxicity
Bernhard University of Virginia Charlottesville

R01-CA-30015 C-Reactive Protein Regulation of Tumor Immunity
Mortensen Ohio State University

R01-CA-30114 Complement Membrane Attack Proteins
Sundsmo Scripps Clinic and Research Foundation

R01-CA-30651 Monocyte Tissue Factor: In Vivo and In Vitro Modulation
Edwards University of Connecticut Health Center

R23-CA-30669 Growth and Differentiation of Mast Cells and T Cells
Yung Sloan Kettering Institute for Cancer Res.

R23-CA-30988 Tumor Specific Helper Factor(s)
Mathews Loyola University Medical Center

TUMOR RELATED ANTIBODIES

R01-CA-15064 Immunochemical Studies on Carcinogenic Mycotoxins
Chu University of Wisconsin Madison

R01-CA-15333 Rheumatoid Factor and Tumor-Host Interaction
Twomey Baylor College of Medicine

R01-CA-16328 Polyamine Radioimmunoassay Studies in Cancer
Campbell University of Oregon Hlth. Sciences Ctr.

R01-CA-20045 Antibody Mediated Cell-Cell Interactions
Phillips-Quagli New York University

R01-CA-20075 Antibody Affinity in Immune Response and Tolerance
Siskind Cornell University Medical Center

R01-CA-23028 Molecular Studies of the Immune Response
Richards California Institute of Technology

R01-CA-23967 Radiolabeled Antibody Tumor Localization
Buchsbaum University of Minnesota of Minneapolis-St. Paul

R01-CA-24329 Monoclonal Antibodies to Human Cell Surface Antigens
Ferrone Scripps Clinic and Research Foundation

R01-CA-25958 Organ Specific Tumor Localizing Antibody
Bale Georgia Institute of Technology

R01-CA-26882 Antibody Responses of Tumor Bearers to Their Tumors
Klein University of Florida

R01-CA-28149 Immunotherapy of a Mouse B Cell Leukemia (BCL1)
Vitetta University of Texas Hlth. Sci. Ctr. Dallas

R01-CA-29876 Human Hybridoma Antibodies in Neoplastic Disease
Kaplan Stanford University

R01-CA-29885 Tumor Cells Escape from Immune Effector Mechanisms
Kuo University of Tenn. Center Health Scien.

R01-CA-29889 Targeting Antibody-Toxin Conjugates to Leukemia Cells
Houston University of Kansas Lawrence

R01-CA-30313 New Approaches to the Therapy of a B Cell Leukemia
Slavin Hadassah University Hospital

R01-CA-30647 In Vitro Synthesis of Human Antibodies to Oncofetal AG
Irie University of California Davis

R01-CA-30663 Antibody-Directed Tumor Specific Chimeric Toxins
Collier University of California Los Angeles

R01-CA-30990 Monoclonal Antibodies to Human Lung Carcinoma Antigens
Bell Washington University

IMMUNOBIOLOGY OF SARCOMAS, CARCINOMAS, AND MELANOMAS

R01-CA-14462 Properties of Lymphoid Tumor Cells In Vivo and In Vitro
Thorbecke New York University

R01-CA-19753 Mixed Leukocyte Tumor Reaction in Syngeneic Systems
Bonavida University of California Los Angeles

R01-CA-20364 Immunodiagnosis of Melanoma
Seigler Duke University

R01-CA-23891 Immunobiology of ASV Induced Primary Brain Tumors
Roszman University of Kentucky

R01-CA-25214 Immunological Studies of Herpes Induced Fibrosarcoma
Gusdon Wake Forest University

R01-CA-26226 Childhood Neuroblastoma: Antigenic Characteristics
Casper Medical College of Wisconsin

R01-CA-27134 Immunobiology of Human Malignant Melanoma
Pickering Louisiana State Univ. Med. Ctr. Shreveport

R01-CA-28311 Immunobiology of Murine Primary Rous Sarcoma
Haughton University of North Carolina Chapel Hill

R01-CA-28611 Teratocarcinoma Tumor Associated Fetal Embryonic Antigen
De Wolf Sidney Farber Cancer Institute

R01-CA-29007 Melanoma Surface Antigens and Cytotoxic T Cells
Oettgen Sloan Kettering Institute for Cancer Res.

R01-CA-30461 Clonal Analysis of Cellular Immune Response in Melanoma
Mukherji University of Connecticut Health Center

P01-CA-16835	Studies of Monoclonal Gammopathies in Humans	
Kyle		Mayo Foundation
R01-CA-16869	Oncornea Cell Membrane Antigens and Its Therapeutics	
Theilen		University of California Davis
R01-CA-17800	Tumor Immunology	
Winn		Massachusetts General Hospital
R01-CA-18995	Studies of Tumor Dormancy and Emergence	
Wheelock		Thomas Jefferson University
R01-CA-20044	Transplantation Immunology	
Winn		Massachusetts General Hospital
R01-CA-22869	Significance of Tumor Leucocytic Infiltrates	
Kreider		Pennsylvania State Univ. Hershey Med. Ctr.
R01-CA-23024	Allograft Rejection and Enhancement	
Tilney		Harvard University
R01-CA-23477	Immunologic Inhibition of Tumor Growth	
Forbes		Vanderbilt University
R01-CA-23679	Cell Mediated Hyperacute Rejection	
Eichwald		University of Utah
R01-CA-24196	Ultraviolet Carcinogenesis and Immunity	
Fortner		Kansas State University
R01-CA-24215	Mechanisms of Metastasis	
Kim		Roswell Park Memorial Institute
R01-CA-24726	Immune Mechanisms Involved in Tumor Metastasis	
Roholt		Roswell Park Memorial Institute
R01-CA-24728	Tumor Induced Changes in Lymphatic Tissues	
Anderson		Johns Hopkins University
R01-CA-25965	Study of Micrometastasized Stable Murine Tumor Clones	
Ghanta		University of Alabama in Birmingham
R23-CA-27893	Bence Jones Protein Properties and Tubulotoxicity	
Chander		New York Medical College
R01-CA-28060	Immunobiology Metastasis	
Frost		University of California Irvine
R01-CA-28139	The Immunobiology of Tumor Metastasis	
Feldman		Weizmann Institute of Science

R23-CA-30110 Vascular Damage in Skin Allograft and Tumor Rejection
Galli Beth Israel Hospital

R01-CA-30169 Bone Allografts for Surgical Oncology
Friedlaender Yale University

R01-CA-30565 Growth Factor(s) in Nodular Sclerosing Hodgkin's Disease
Newcom University of Oregon Hlth. Sciences Ctr.

R01-CA-31199 Macrophage-Mediated Injury Causing Tumor Regression
Russell University of Florida

R13-CA-31821 International Cancer Congress (UICC)
Mirand

EFFECTS OF DISEASE ON IMMUNE FUNCTION

R01-CA-10267 Immunological Lysis in Neoplastic Disease
Rosse Duke University

R01-CA-14300 Mechanism of Immunosuppression by Plasmacytomas
Havas Temple University

P01-CA-15147 Leukemia--Lymphoma Program
Balcerzak Ohio State University

R01-CA-15334 Cellular Mechanisms in Tumor-Specific Immunity
Smith University of Florida

R01-CA-15462 Cell Interactions in Tumor Immunity
Argyris Upstate Medical Center

R01-CA-15585 A Soluble Mediator of Tumor-Induced Immunosuppression
Zolla-Pazner New York University

R01-CA-17273 The Immune Response to Virally Determined Tumor Antigens
Lamon University of Alabama in Birmingham

R01-CA-17818 Tumor Immunity and Tumor-Host Interactions
Stutman Sloan Kettering Institute for Cancer Res.

R01-CA-18149 Autoimmunity and Neoplasia in New Zealand Black Mice
Siegel University of Oregon Hlth. Sciences Ctr.

R01-CA-18185 Hereditarily Athymic--Asplenic Mice: Tumor Growth
Lozzio University of Tennessee Knoxville

R01-CA-18234 Immunobiology of Primary Intracranial Tumors
Roszman University of Kentucky

P01-CA-19267	Clinical Immunobiology Program Project	
Oettgen		Memorial Hospital for Cancer-Allied Diseases
R01-CA-20543	Antigen-Antibody Complexes in Cancer Patients' Sera	
Rossen		Baylor College of Medicine
R01-CA-20816	The Pathogenesis of Autoimmunity in New Zealand Mice	
Gershwin		University of California Davis
R01-CA-20920	Mechanisms of Carcinogenesis	
Prehn		Jackson Laboratory
R01-CA-23217	Immunologic Regulation of Myeloma Cell Growth	
Lynch		Washington University
R01-CA-23372	Studies on Soluble Antigens on MTV Induced Mammary Tumor	
Laing		Howard University
R01-CA-23500	Prostaglandins and Immunosuppression in Cancer	
Bockman		Sloan Kettering Institute for Cancer Res.
R01-CA-23648	Immunity to Human Ovarian Tumors and Chemotherapy	
Haskill		University of North Carolina Chapel Hill
R01-CA-23709	Induction of Tolerance and Suppressor Cells In Vitro	
Adler		St. Jude Children's Research Hospital
R01-CA-23882	Defective Self-Recognition as a Cause of Cancer	
Neefe		Georgetown University
R01-CA-24244	Studies of the Immunobiology of B-16 Melanoma	
Brody		Downstate Medical Center
R01-CA-24429	Immunosuppressants and Lymphocyte Function	
Winkelstein		Montefiore Hospital
R01-CA-24511	Auto-regulation of Immune Response by Anti-idiotype	
Mayers		New York State Department of Health
R01-CA-24698	Arginine Pulse Labeling of Plasma Cell Neoplasms	
Humphrey		Johns Hopkins University
R01-CA-24725	Factors Negating Response to Mammary Adenocarcinoma	
Lucas		Stanford University
R01-CA-24873	Immunosuppression in Cancer Patients	
Bankhurst		University of New Mexico Albuquerque
R01-CA-24901	Immunomodulation of Oncogenesis	
Outzen		Jackson Laboratory
R01-CA-25072	Suppressor T-Cells in Malignant Lymphoma	
Raich		West Virginia University

R01-CA-25183 Immunologic Factors in Central Nervous System Tumors
Wood University of Kansas Col. Hlth. Sci. & Hosp.

R01-CA-25746 Genetic Mechanisms in Immunologic Deficiency States
Fundenberg Medical University of South Carolina

R23-CA-25932 Thymic Antigens, Tolerance and Self-Recognition
Lattime Sloan Kettering Institute for Cancer Res.

R23-CA-26116 Antigen-Specific Suppression of Antitumor Immunity
Nelson Fred Hutchinson Cancer Research Center

R01-CA-26141 Cell-Mediated Cytotoxicity in Children with Neoplasms
Yu University of California San Diego

R01-CA-26169 Immunosuppression During Acute Avian Leukemia
Bose University of Texas Austin

R01-CA-26268 Anti-II Antibodies and II Antigens in Carcinomas
Dube Evanston Hospital

R01-CA-26447 Pathogenesis of Preleukemic Aplastic Anemia
Hoover Ohio State University

R01-CA-26760 Monocyte-Lymphocyte Interactions in Mycosis Fungoides
Weston University of Colorado Hlth. Sciences Center

R01-CA-26861 Determination of Malignant Potential of Cultured Cells
Giovanella Stehlin Foundation for Cancer Research

R01-CA-27168 Histamine Receptor Positive T-Cells in Cancer
Osband University Hospital

R01-CA-27390 Ethylnitrosourea-Induced Rat Gliomas
Spence University of Washington

R01-CA-28167 Tumor Enhancement in Lectin Treated Mice
Ekstedt Northwestern University

R23-CA-28433 Identification of AG Specific Suppressor Cells in Man
Ostenson Fred Hutchinson Cancer Research Center

R01-CA-29200 Autologous Immunity to Human Cultured Melanoma
Guerry University of Pennsylvania

R01-CA-29752 Immune Response Modulation by Tumor Promoter
Devens University of California Riverside

R01-CA-29906 Mechanisms of Immunoregulation in Human Cancer
Kadish Yeshiva University

R01-CA-30020 The Cell Surface Phenotype of Malignant Lymphoma
Aisenberg Massachusetts General Hospital

R01-CA-30088 Synergy of Tumor Chemotherapy and Host Immunity
Dray University of Illinois Medical Center

R23-CA-30160 Cytotoxic and Suppressor Cells in the Chicken
Chi East Tennessee State University

R01-CA-30187 Regulation of Cell-Mediated Cytotoxicity Mechanisms
Bloom University of California Los Angeles

R01-CA-30457 Immunoregulation of Human Tumor Growth in Nude Mice
Koros University of Pittsburgh

R01-CA-30660 Immunoregulatory Dysfunctions in Non-Hodgkin's Lymphoma
Keller Medical College of Wisconsin

R01-CA-30920 Immunosuppression in Murine Chronic Lymphocytic Leukemia
Uhr University of Texas Health Science Center Dallas

R01-CA-30933 Immunomodulatory Factors in Head and Neck Cancer
Veltri West Virginia University

R01-CA-31226 Tolerance and Immunity to Avian RNA Tumor Viruses and VI
Meyers Mayo Foundation

R01-CA-31336 Antigen Evasion as a Tumor Escape Mechanism
Stackpole New York Medical College

R01-CA-31837
Prehn Santa Clara Valley Medical Center

IMMUNOTHERAPY-MECHANISM RATHER THAN THERAPEUTIC RESULT

R01-CA-11605 Immunological Reactivity in Special Circumstances
Simmons University of Minnesota at Minneapolis

R01-CA-18047 Irradiation and Marrow Transplantation in Large Animals
Thomas University of Washington

R01-CA-26138 Immune Testing in Lung Cancer During Immunotherapy
Harris Rush University

R01-CA-26162 Mechanism of Nanaase-enhanced Tumor Immunogenicity
Pincus SRI International

R01-CA-26738 Cellular Immunity to Tumors
Zarling University of Minnesota of Minneapolis-St. Paul

R01-CA-27625 Hybrid Tumor Cell Immunotherapy
McCune University of Rochester

R01-CA-28441 Extracorporeal Immunoadsorbents in Immunotherapy
Terman Baylor College of Medicine

R01-CA-28941 Resistance and Sensitization-Role of Lymphocyte Subsets
Deeg Fred Hutchinson Cancer Research Center

R01-CA-29328 Control of Graft-Versus-Host Disease
Parkman Sidney Farber Cancer Institute

R01-CA-31787 Irradiation and Marrow Transplantation in Large Animals
Thomas Fred Hutchinson Cancer Research Center

LYMPHOCYTES

R01-CA-03367 Immunogenetic Resistance to Lymphoma-Leukemia
Trentin Baylor College of Medicine

R01-CA-08593 Immune Responses to Tumor Grafts
Gershon Yale University

P01-CA-12800 Immune Functions and Cancer
Fahey University of California Los Angeles

R01-CA-12844 Controls of Proliferation Specific for Leukemias
Cudkowicz State University of New York at Buffalo

R01-CA-13396 Immunogenesis from Bone Marrow Cells
Miller Michigan State University

R01-CA-14049 Cell-Mediated Immunity to Ascites Tumors
Amos Duke University

R01-CA-14216 Characterization of Lymphoid Populations in Cancer
Gershon Yale University

P01-CA-14723 Study of Experimental Cancer Immunology
Benacerraf Harvard University

P01-CA-15822 Immunobiology of Normal and Neoplastic Lymphocytes
Wilson University of Pennsylvania

P01-CA-16247 Immunologic Resistance to Cancer
Lawrence New York University

R01-CA-16271 Regulatory Signals in Cytotoxic T-Cell Development
Faanes Sloan Kettering Institute for Cancer Res.

R01-CA-16367 Lymphocytes: Gene Expression and Activation Events
Sell University of California San Diego

P01-CA-16673 Cell Differentiation Studies in Cancer Immunobiology
Cooper University of Alabama in Birmingham

R01-CA-16885 Propagation of Thymus-Derived Lymphocyte Lines
Ruddle Yale University

R01-CA-17013 Lymphocyte Sensitization to Tumor Antigens In Vitro
Golub University of California Los Angeles

P01-CA-17404 Immunobiology, Immunodeficiency, and Cancer
Choi Sloan Kettering Institute for Cancer Res.

R01-CA-17531 Mechanism and Uses of Anti-Ig Immunosuppression
Manning University of Wisconsin Madison

R01-CA-17673 Regulation of Immunity by Antibody and B-Cells
Hoffmann Sloan Kettering Institute for Cancer Res.

R01-CA-17733 Lymphocyte Antigens: Structure, Function and Synthesis
Trowbridge Salk Institute for Biological Studies

R01-CA-19170 Mechanisms of BCG-Mediated Suppression of Tumor Growth
Bernstein Fred Hutchinson Cancer Research Center

R01-CA-19334 Antigen Receptor of Continuous T Killer Cell Line
Dennert Salk Institute for Biological Studies

R01-CA-20105 Information from Immunological Reaction Tables
Wohlgemuth University of Maine at Orono

R01-CA-20169 Long-Lived Lymphocytes and Secretory Bursal Cells
Glick Mississippi State University

R01-CA-20823 Lymphocyte Production and Traffic in the Bone Marrow
Rosse University of Washington

R01-CA-21401 Studies of Isolated Marrow-Dependent M Cells
Kumar Boston University

P01-CA-21825 Self-Nonself Discrimination and Tumor Recognition
Grey National Jewish Hospital & Research Ctr.

R01-CA-22093 Functions of Atypical Lymphocytes
Hutt-Fletcher University of North Carolina Chapel Hill

R01-CA-22126 Ultraviolet Light Radiation and Immunoregulation
Daynes University of Utah

R01-CA-22241 Lymphocyte Subsets in Immune-Deficiency States
Scheid Sloan Kettering Institute for Cancer Res.

R01-CA-22268 Genetic Aspects of Tumor Host Immune Relationship
Warner University of New Mexico Albuquerque

R01-CA-22544	Lymphocyte Responses to Syngeneic Antigens	
Ponzio		Northwestern University
R01-CA-22677	Pathobiology of Myeloma and Anti-idiotypic Immunity	
Schreiber		University of Chicago
R01-CA-22786	Receptor Dynamics and Normal/Tumor Cell Function	
Bankert		Roswell Park Memorial Institute
R01-CA-22845	Immune Response to Modified Self and Tumor Antigens	
Scott		Duke University
R01-CA-23025	Comparative Transplantation Immunogenetics	
Hildemann		University of California Los Angeles
R01-CA-23262	DNA Polymerases in Normal and Leukemic Lymphoid Cells	
Bollum		U.S. Uniformed Services Univ. of Hlth. Sci.
R01-CA-23354	Natural Tumor Cell Killing in Humans	
Koren		Duke University
R01-CA-23593	Response of Leukocytes to Human Tumor Cells	
Sanderson		University of Colorado Hlth. Sciences Ctr.
R01-CA-24335	Lectin-Dependent Cell-Mediated Cytotoxicity	
Laux		University of Rhode Island
R01-CA-24338	In Vitro Studies of Normal and Neoplastic Lymphocytes	
Fu		Rockefeller University
R01-CA-24368	Immunobiology of Early Lymphocyte Development	
Sato		Harvard University
R01-CA-24431	Cellular and Structural Basis of Immunological Tolerance	
Benjamin		University of Virginia
R01-CA-24436	Receptor Function in Lymphocyte Differentiation	
Wofsy		University of California Berkeley
R01-CA-24438	Genetic Control of Allotype Expression of Human Ig	
Litwin		Cornell University Medical Center
R01-CA-24442	Chemical Basis for Receptor Recognition of Lysozymes	
Sercarz		University of California Los Angeles
R01-CA-24450	T-Cell Receptor and Effector Molecules	
Redelman		University of California San Diego
R01-CA-24472	Development of Thymic Lymphocytes	
Basch		New York University
R01-CA-24537	Murine Effector Cells	
Henney		Fred Hutchinson Cancer Research Center

R01-CA-24607	HLA Restricted Suppressor T Cells of Mixed Lymphocytes	
Engleman	Stanford University	
R01-CA-25054	Cellular Mechanisms Regulating Antibody Production	
Mullen	University of Missouri Columbia	
R01-CA-25250	Natural Killer Cells: Genetic Control and Role	
Klein	Caroline Institute	
R01-CA-25253	Immunoregulatory Network Probed by Cell Hybridization	
Bankert	Roswell Park Memorial Institute	
R01-CA-25416	Immunogenetics of NK-1+ Natural Killer Cells	
Koo	Sloan Kettering Institute for Cancer Res.	
R01-CA-25508	Ontogenetic Relationship of CR+ and CR- B Lymphocytes	
Hammerling	Sloan Kettering Institute for Cancer Res.	
R01-CA-25583	Cell Mediated Immunity in Mouse Mammary Tumor Models	
Lopez	University of Miami	
R01-CA-25612	Immunological Effects on Tumor Growth, and Rejection	
Plate	Rush-Presbyterian-St Lukes Medical Ctr.	
R01-CA-25738	T Cell Differentiation: Molecular Mechanisms	
Scheid	Sloan Kettering Institute for Cancer Res.	
R01-CA-25747	Histocompatibility Antigens in Defined Membranes	
Gilmer	Florida State University	
P01-CA-25803	Control of Normal and Abnormal Cell Development	
Katz	Scripps Clinic and Research Foundation	
R01-CA-26084	Interactions Between Tumor Cells and T Lymphocytes	
Hale	Wake Forest University	
R01-CA-26257	Modulation of Lymphocyte Cytolysis of Tumor Cells	
Fuson	University of Tennessee Knoxville	
R01-CA-26284	Regulation of Adenosine Deaminase in Human Cells	
Daddona	University of Michigan	
R01-CA-26467	Effector and Suppressor Mechanisms of Tumor Immunity	
Stout	Brandeis University	
R01-CA-26480	Antitumor Activity of Tumor-Bearer Lymphoid Cells	
Dray	University of Illinois Medical Center	
R01-CA-26695	Antigen-Specific T-Cell Clones: Generation and Analysis	
Cantor	Sidney Farber Cancer Institute	
R01-CA-26713	Genetics and Regulation of Cell-Mediated Cytotoxicity	
Clark	University of Washington	

R23-CA-27115 Characterization of Natural Killer Cells
Tai University of New Mexico

R23-CA-27552 Cytotoxic T Cells to Syngeneic MuLV+ Tumors
Green Fred Hutchinson Cancer Research Center

R01-CA-27691 Immunoregulation by T Cell Subsets in Myeloma and CLL
Ozer Roswell Park Memorial Institute

R01-CA-27772 In Vitro Immunization to Human Tumor Cells
Sharma University of California Irvine

R01-CA-27854 Cell Surface Carbohydrate and Lymphocyte Interactions
Bell University of Rochester

R01-CA-27915 Antibody Dependent Cell Cytotoxicity Reactions
Fanger Case Western Reserve University

R01-CA-28099 F.A.C.S. of Immunologic Components
Amos Duke University

R01-CA-28196 Proteinases of Human Natural Killer Cells
Hudig University of California San Diego

R01-CA-28332 In Situ Anti-tumor Immunity and Effects of Radiation
Lord University of Rochester

R01-CA-28533 Mechanisms of Tumor Destruction by Immune Effectors
Russell Washington University

R01-CA-28708 Immunoregulation of Myeloma Cell Differentiation
Rohrer University of South Alabama

P01-CA-28900 Control of Antigen-Specific T Cell Responses
Eisen Massachusetts Institute of Technology

R01-CA-28936 Immunoregulation in Autoimmunity and Malignant Disease
Haynes Duke University

R01-CA-29208 Fc Receptor-Bearing T Lymphocytes in Murine Myeloma
Lynch Washington University

R23-CA-29224 Cytotoxic T Lymphocyte Lines to Murine Plasmacytomas
Giorgi University of New Mexico Albuquerque

R01-CA-29282 Prothymocyte Maturation and Function
Waksal Tufts University

R01-CA-29594 Lymphoid Cell Purine Nucleoside Phosphorylase
Catsimpoolas Boston University

P01-CA-29606 Immunoregulation: Studies on T Cells and Their Products
Gershon Yale University

R01-CA-29635 Analysis of Human T Lymphocyte Subsets Grown In Vitro
Pauly Roswell Park Memorial Institute

R23-CA-29803 Cytotoxic Cell Responses to Non-H2 Antigens
MacPhail Sloan Kettering Institute for Cancer Res.

R01-CA-30147 Genetic Markers, Leukemogenesis and Thymic Function
Gottlieb University of Texas Austin

R23-CA-30183 Bone Marrow Cytotoxic Precursor T Cells
Klimpel University of Texas Med. Br. Galveston

R23-CA-30188 Autorecognition and Immunoreactivity
Scheffel Marquette University

R01-CA-30280 T-Lymphocyte Regulated Tumor Cell Killing by Neutrophils
Weisbart University of California Los Angeles

R01-CA-30972 Marrow Prostaglandins and T-Cell Differentiation
Bockman Sloan Kettering Institute for Cancer Res.

R13-CA-31141 "Host Defense in Neoplasia" (1981 Gordon Conference)
Dvorak Beth Israel Hospital

R13-CA-31191 Int'l Workshop in Mechanisms in Cell-Mediated Cytotoxicity
Clark University of California Los Angeles

R13-CA-31451 Midwest Autumn Immunology Conference
Schmidtke Eli Lilly and Company

R23-CA-31591 Regulation of Human B Cell Proliferation
Yen University of Iowa

MONOCYTES AND MACROPHAGES

R01-CA-14113 Tumor Defense by Platelets and Macrophages
Shin Johns Hopkins University

R01-CA-15236 Macrophage Recognition and Tumor Cell Interactions
Schreiber University of Pennsylvania

R01-CA-16652 Macrophage Functions in Tumorigenesis
Walker St. Jude Children's Research Hospital

R01-CA-16784 Tumoricidal Effects of Macrophages: Pathologic Study
Adams Duke University

R01-CA-18672 The Role of Macrophage Subclasses in Tumor Immunity
Fishman St. Jude Children's Research Hospital

R01-CA-19052 Development and Function of Activated Macrophages
Moore Sloan Kettering Institute for Cancer Res.

R01-CA-20822 Cell Interaction and the Clotting System
Colvin Massachusetts General Hospital

R01-CA-21225 Macrophage Activation by Lymphocyte Mediators
Remold-O'Donnel Center for BLood Research

R01-CA-22090 Mononuclear Leukocytes in Tumor Immunity
Náthan Rockefeller University

R01-CA-23503 Mechanisms of Macrophage Antitumor Activation
Edelson Children's Hospital Medical Center

R01-CA-24686 Macrophage Extrinsic Activity Vs Viruses
Morahan Virginia Commonwealth University

R01-CA-25052 Immune Responses In Vitro-H-2 (IR) Locus Function
Niederhuber University of Michigan

R23-CA-26158 The Immunogenetics of Macrophage Suppression in Man
Stux Sidney Farber Cancer Institute

R01-CA-26824 Mononuclear Phagocytes in Human Ovarian Carcinoma
Mantovani Mario Negri Institute Pharmacologic Res.

R01-CA-26846 Mechanism of Human Monocyte Differentiation
Musson National Jewish Hospital & Research Ctr.

R01-CA-26996 Characterization and Functional Studies of "A" Cells
Fishman St. Jude Children's Research Hospital

R01-CA-27070 Macrophage Tumor Cell Killing and Red Cell Catabolism
Weinberg Duke University

R01-CA-27523 Macrophages and Regulation of Tumor Growth
Evans Jackson Laboratory

R01-CA-27694 Cytotoxic Macrophages Activation and Target Recognition
Tompkins University of Illinois Urbana-Champaign

R01-CA-28308 Differentiation and Anti-tumor Activity of Macrophages
Kaplan Virginia Commonwealth University

R23-CA-28935 Macrophage Mediated Tumor Cytotoxicity
Cameron Medical University of South Carolina

R01-CA-29266 Characterization of Monocyte Subsets in Blood
Weiner University of Florida

R23-CA-29333 Metabolic Events Related to Macrophage Activation by MVE
Klykken Virginia Commonwealth University

R01-CA-29336 Macrophage-Mediated Cytotoxicity of Tumor Targets
Erickson University of California Davis

P01-CA-29589	Macrophage Activation: Development and Regulation	
Adams		Duke University
P01-CA-30198	Human Mononuclear Leukocytes in Cancer	
Silverstein		Rockefeller University
R23-CA-30631	Targets of a Leukosis Virus Infection	
Price		Trenton State College
R01-CA-31202	Monoclonal Antibody Depletion of Macrophages In Vivo	
Russell		University of Florida

MALIGNANCIES OF THE IMMUNE SYSTEM (LYMPHOMA/LEUKEMIA)

R01-CA-03367	Immunogenetic Resistance to Lymphoma-Leukemia	
Trentin		Baylor College of Medicine
R01-CA-08975	Human Leukemia Associated Antigens	
Metzgar		Duke University
R01-CA-10018	Experimental Model of Malignant Lymphoma	
Schwartz		New England Medical Center Hospital
R01-CA-12779	Leukocyte Regulatory Mechanisms	
Nowell		University of Pennsylvania
R01-CA-13701	Mechanisms of Immunity in Leukemia	
Murphy		University of Michigan
R01-CA-14413	Study of Human Lymphatic Neoplasia	
Minowada		Roswell Park Memorial Institute
R01-CA-15472	Immunity to Myeloma Tumors	
Eisen		Massachusetts Institute of Technology
R01-CA-17276	Membrane Antigens from Normal and Leukemic Lymphocytes	
Pressman		Roswell Park Memorial Institute
R01-CA-18602	Immunocompetent Cells in Acute Lymphocytic Leukemia	
Casper		Medical College of Wisconsin
R01-CA-20499	Immunobiology of Cutaneous T Cell Lymphomas	
Edelson		Columbia University
R01-CA-21062	NK Cells in Resistance to Marrow Transplantation	
Lotzova		University of Texas System Cancer Center
R01-CA-21900	Protective T-Cell Subpopulation Responses in Leukemia	
Duffey		University of Texas Hlth. Sci. Ctr. San Antonio
R01-CA-22948	Gene Mechanisms in Lymphoma and Lymphoproliferation	
Murphy		Jackson Laboratory

R01-CA-23770 Antigen Induced Lymphoma of Mice
Haughton University of North Carolina Chapel Hill

R01-CA-24679 Extra-nodal Lymphomas: Immunology and Ultrastructure
Knowles Columbia University

R01-CA-24950 A Thymus Determined Mechanism of Leukemia Resistance
Datta Tufts University

R01-CA-25097 Differentiation of Immune System: Cell Surface Antigens
Kersey University of Minnesota at Minneapolis

R01-CA-25369 Human Leukemia Antigens: Isolation and Characterization
Schlossman Sidney Farber Cancer Institute

R01-CA-25391 Immunological Control of Dormant Leukemia
Dietz Michigan Cancer Foundation

R01-CA-25411 SJL Mice Lymphomagenesis as a Model of B-Cell Lymphoma
Ford University of Texas System Cancer Center

R01-CA-25613 Membrane Components of Normal and Leukemic Leukocytes
Ross University of North Carolina Chapel Hill

R01-CA-25873 Membrane Proteins of Human Leukemias and Lymphomas
Humphreys University of Massachusetts Medical School

R01-CA-26369 T-MICG and N-MICG in Lymphoid Malignancy
Hauptman Thomas Jefferson University

R01-CA-26945 Detecting Paul-Bunnell Antigen in Lymphoma and Leukemia
Fjelde New York State Department of Health

R01-CA-27416 Characterization of New Human IA and Leukemia Antigen
Mohanakumar Virginia Commonwealth University

R23-CA-27542 T Cell Subsets and Marek's Disease Viral Oncogenesis
Fredericksen New York University

R01-CA-27690 Multiple Cell Marker Analysis in Hematopoietic Tumors
Koziner Sloan Kettering Institute for Cancer Res.

R01-CA-27826 Manipulation of Antitumor Immunity In Vitro
Bach University of Minnesota of Minneapolis-St. Paul

R01-CA-27942 Role of the Spleen in the Growth of a B Cell Leukemia
Strober Stanford University

R01-CA-28416 Receptors for Immunoglobulin on Human Lymphoma-Leukemia
Rudders New England Medical Center Hospital

R01-CA-28504 T Cell Growth and Differentiation in Leukemia
Chiao Sloan Kettering Institute for Cancer Res.

R01-CA-28746	Cell Surface Antigens in Neoplastic and Autoimmune Disease	
Fox		Scripps Clinic and Research Foundation
R01-CA-29655	Cytogenetic Studies of Human Myeloma	
Mackenzie		University of California Davis
R01-CA-29964	UNC-CH Immunocytomas	
Haughton		University of North Carolina Chapel Hill
R23-CA-30895	Differentiation of Murine B Cell Lymphomas	
Lanier		University of New Mexico Albuquerque
R01-CA-31792	Immunobiology of Viral Leukemia and Its	
Bennett		University of Texas Hlth. Sci. Ctr. Dallas

IMMUNE SURVEILLANCE

R01-CA-11898	Brain Tumors: Virological and Immunological Studies	
Bigner		Duke University
R01-CA-12461	Suppression of Established Leukemia Virus Infections	
Wheelock		Thomas Jefferson University
R01-CA-13339	Host Defense Against Lymphoblastic Leukemia	
Weksler		Cornell University Medical Center
R01-CA-15988	Immune Surveillance and Cancer	
Stutman		Sloan Kettering Institute for Cancer Res.
R01-CA-16136	The Role of Rabbit Lymphoid Cells in Tumor Immunity	
Sell		University of California San Diego
R01-CA-19754	Immunoselection and Cancer: A Problem in Evolution	
Cohn		Salk Institute for Biological Studies
R01-CA-20408	Immunodeficiency and Tumorigenesis	
Shultz		Jackson Laboratory
R01-CA-20833	Cell-Mediated Cytotoxicity in Humans	
Trinchieri		Wistar Institute of Anatomy and Biology
R01-CA-21360	Subversion of Immune Mechanisms in Malignant Tumors	
Spitalny		Trudeau Institute
R01-CA-22517	Monocyte Function in Neoplasia	
Normann		University of Florida
R01-CA-22720	H-2 Complex and Susceptibility to Mammary Tumor Virus	
Long		Sidney Farber Cancer Institute
R01-CA-23809	Natural and Tissue-Specific Immunity to Human Neoplasms	
Saksela		University of Helsinki

R01-CA-24443	Immunology of Germfree Genetically Thymusless Mice	
Reed		University of Montana
R01-CA-24497	Immunogenetic Analysis of Rous Sarcoma Development	
McBride		Baylor College of Medicine
R01-CA-24608	Tumor Immunity and Leukemia	
Grant		Harvard University
R01-CA-25165	Specific Immunity and Prognosis in Breast Cancer	
Black		New York Medical College
R01-CA-25384	Natural and Antibody-Dependent Cellular Cytotoxicity	
Kim		Sloan Kettering Institute for Cancer Res.
R01-CA-25686	Epstein-Barr Virus: Effects on Human Lymphocytes	
Sumaya		University of Texas Hlth. Sci. Ctr. San Antonio
R01-CA-25917	Cellular and Genetic Aspects of Antitumor Immunity	
Daynes		University of Utah
R23-CA-25944	Relationship of Leukemogenesis and Immune Responsiveness	
Johnson		Jackson Laboratory
R01-CA-26144	Leukocyte Adherence Inhibition Assay in Human Cancer	
Powell		Case Western Reserve University
R01-CA-26344	Autologous Lymphocyte Reactions and Immune Surveillance	
Weksler		Cornell University Medical Center
R01-CA-26752	Relevance and Functions of Natural Killer Cells	
Wigzell		University of Uppsala
R01-CA-26782	In Vivo Role of Natural Killer Cells	
Kiessling		Caroline Institute
R01-CA-26799	Immunological Reactivities and MTV Infections	
Tagliabue		Mario Negri Institute Pharmacologic Res.
R01-CA-26942	H-2 Linked Resistance to Tumor: Effectors and Targets	
Fuji		New York State Department of Health
R01-CA-27599	Genetic Control of Resistance and Immunity to P815	
Williams		Northwestern University
R01-CA-28231	H-2 Associated Natural Resistance	
Carlson		Jackson Laboratory
R01-CA-28834	Basophil/Mast Cell Function in the Control of Cancer	
Dvorak		Beth Israel Hospital
R01-CA-29355	T-Cell Nonresponsiveness in Gross Virus-Infected Mice	
Blank		University of Pennsylvania

R01-CA-29910 Human NK Cells, Interferon(s) and Leukemia/Lymphoma
Pattengale University of Southern California

R01-CA-30115 Immune Reactivity to Primary Sarcomas in Mice
Babcock University of Texas Hlth. Sci. Ctr. Houston

R01-CA-31836
Prehn Santa Clara Valley Medical Center

IMMUNOTHERAPY IN ANIMAL MODELS

R01-CA-15446 Antigen-Antibody Interactions in Neoplastic Disease
Minden National Jewish Hospital & Research Ctr.

R01-CA-16642 Immunological Basis of Tumor Regression
North Trudeau Institute

R23-CA-25668 Induction of Genetically Tailored Immune Imbalance
Leech Louisiana State Univ. Med. Ctr. New Orleans

R01-CA-27794 Mechanisms of Endotoxin-Induced Tumor Regression
North Trudeau Institute

R01-CA-30303 Selective Stimulation of Cell Mediated Cancer Immunity
Hunter Emory University

R23-CA-30686 Ex Vivo Immunosorption as Tumor Therapy
Jones Sloan Kettering Institute for Cancer Res.

BONE MARROW TRANSPLANTATION

R01-CA-20044 Transplantation Immunology
Winn Massachusetts General Hospital

R01-CA-20484 Specific Adoptive Immunotherapy of AKR Leukemia
Bortin Mount Sinai Medical Center

R01-CA-23602 Bone Marrow Transplantation After Ly Subset Elimination
Krown Sloan Kettering Institute for Cancer Res.

R01-CA-23678 Tolerance of Bone Marrow Grafts
Click University of Minnesota of Minneapolis-St. Paul

R01-CA-26245 Mechanisms of Successful Adoptive Immunotherapy
Truitt Mount Sinai Medical Center

R01-CA-28701 Chronic Graft-Versus-Host Disease in Radiation Chimera
Beschorner Johns Hopkins University

R01-CA-29592
Kahan

Active Specific Immunotherapy in Man: A Murine Model
University of Texas Hlth. Sci. Ctr. Houston

UNCLASSIFIED

R23-CA-29155
Locke

Stress and Human Cell-Mediated Immunity
Beth Israel Hospital

CONTRACT RESEARCH SUMMARY

Title: Induction of Colonic Tumors in Guinea Pigs

Principal Investigator: Dr. Gary L. Cockerell
Performing Organization: Cornell University
City and State: Ithaca, NY

Contract Number: NO1-CP-65744
Starting Date: 9/30/76 Expiration Date: 3/29/81

Goal: To produce carcinomas of the colon in approximately 700 NIH guinea pigs and subsequently test the immunotherapeutic effect of BCG vaccines versus other modalities of treatment.

Approach: N-methyl-nitrosourea is administered by intrarectal installation to produce colonic carcinomas. Following tumor induction, laparotomies are performed, and the tumorous portion of bowel is (1) injected intralesionally with BCG vaccines, (2) surgically resected and a diverting colostomy established, or (3) located but not otherwise treated. Animals are then allowed to recover from surgery and are observed until death.

Progress: Two sets of 240 guinea pigs each were exposed to the intrarectal administration of methylnitrosourea (MNU) for 14 to 35 weeks to induce colonic adenocarcinomas. At 24, 28 or 35 weeks post start of MNU administration, groups of guinea pigs were treated either by intratumoral injection of BCG or surgical excision of tumors and compared to non-treated animals. Most guinea pigs died within one year of therapy and there was no difference in survival rate between treated and non-treated groups. The leukocyte migration inhibition assay, lymphocyte blast transformation assay with variations reaction, and macrophage cytotoxicity assays have been used to evaluate the immune reactivity of MNU-exposed guinea pigs. Macrophage cytotoxicity has been the only assay to yield useable results but there are yet insufficient therapeutic modalities. A third set of 240 guinea pigs has been exposed to lesser amounts of MNU to derive carcinogen dose response data. These data will make it possible to examine the effects of immunotherapy of surgical treatment on tumors which arise in a smaller percent of MNU-exposed animals and which might therefore be less malignant.

Significance to Cancer Research: The guinea pig colon carcinoma model will serve as a useful system to test various methods of tumor treatment, since it has now been shown that the guinea pig colon tolerates intramural BCG injection and is surgically resectable.

Project Officer: Ms. Judith Whalen
Program: Immunology Section
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Long-term Tumor-specific Cytotoxic Lymphocytes in Treatment of Mouse Leukemia

Principal Investigator: Dr. Kendall A. Smith
Performing Organization: Dartmouth Medical School
City and State: Hanover, NH

Contract Number: NO1-CB-74141
Starting Date: 9/30/77 Expiration Date: 9/29/81

Goal: To evaluate the usefulness of tumor-specific cytotoxic lymphocytes maintained in continuous culture for the prevention and treatment of mouse leukemia.

Approach: Attempts will be made to (1) demonstrate the tumor-antigen reactivity of human and murine cytotoxic T-cell lines; and (2) test in vivo the immunoprophylactic and immunotherapeutic value of murine cytotoxic T cells (CTLL) maintained in continuous proliferative culture.

Progress: Preliminary experiments show that murine CTLL (1×10^7 cells) may be effective in prolonging survival when administered three days after a lethal IV dose (1×10^3 cells) of leukemic cells. Progress was made toward the construction of a murine model to test the use of CTLL for the eradication of leukemia cells prior to autologous bone marrow infusion in mice which receive lethal irradiation. The investigators report that the supplementation of cultures comprised of normal unprimed murine spleen cells and syngeneic tumor cells with partially purified, lectin-free TCGF leads to the generation of a primary in vitro cytotoxic response. Based on his data, the investigator has constructed a model which depicts the biological role of TCGF in the T-cell immune response.

Significance to Cancer Research: The ability to cultivate large quantities of tumor-specific cytotoxic lymphocytes which retard in vivo tumor growth may provide a new approach to cancer treatment. The successful culture of differentiated functional T cells for extended periods offers the promise of new understanding of the mechanisms of cellular immunity and of immunodeficient and hyperimmune disease states.

Project Officer: Harriet L.G. Gordon, M.D.
Program: Immunology Section
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Characterization of Antigen-binding T-cell Receptors

Principal Investigator: Dr. P.H. Krammer
Performing Organization: Institute for Immunology
City and State: Heidelberg, Germany

Contract Number: NO1-CB-74179
Starting Date: 9/30/77 Expiration Date: 3/31/81

Goal: To test for the expression of alloantigen receptors on murine T-cell tumors.

Approach: Use AKR/J lymphomas; develop sensitive assay systems for alloantigen binding T-cell receptors; obtain sufficient quantities of receptor material from positive tumors to perform biochemical analyses.

Progress: Assays for proliflerative and cytotoxic T cell responses have been standardized. Utilization of these assays permits rapid screening of a large number of continuous lines of normal cytotoxic T cells for receptor expression. The specificity of two idiotype systems have been established, using this assay and other techniques. Anti-idiotypic antisera made in (AKRxC57Bl/6)F1 mice against AKR anti-C57Bl/6 MLR activated T cell blasts recognizes AKR T cell receptors for C57Bl/6 alloantigens. Anti-idiotypic antisera made in syngeneic AKR mice against AKR anti-TNP activated T cell blasts (containing AKR anti-TNP H-2 restricted cytotoxic T cells) recognizes idiotypes on T cell receptors of AKR cells cytotoxic for syngeneic TNP coupled target cells. Over fifty AKR T cell lines have been established in tissue culture for several months, growing in the presence of interleukin 2 (T cell growth factor). These lines have been cloned by limiting dilution and are derived from primary anti-TNP activated lymphocytes. The contractor spent the remaining contract period increasing the number of growing clones, testing and selecting them for anti-TNP specificity.

Significance to Cancer Research: T cells play a decisive role in tumor defense. The recognition process of the T cell in general and the recognition of tumor targets in particular are not understood at all. One clue to this understanding is the biochemical nature of the T-cell antigen recognition system.

Project Officer: Ms. Judith M. Whalen
Program: Immunology Section
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Genetic Control of Susceptibility to Tumors

Principal Investigator: Dr. Chen K. Chai
Performing Organization: Jackson Laboratory
City and State: Bar Harbor, ME

Contract Number: NO1-CB-74181
Starting Date: 9/30/77 Expiration Date: 2/28/81

Goal: Elucidate the reasons why $\underline{A}^{y}$ mice are more susceptible to lung tumors than $\underline{aa}$ mice.

Approach: Study the carcinogenic responses of the homozygotes and heterozygotes for the different yellow and non-yellow alleles at the agouti locus.

Progress: A study was made on the response to urethane for lung tumor production in mice of 20 genotypes for 6 alleles at the agouti locus. The mean number of lung tumors was the highest in the $\underline{A}^{y}\underline{A}^{w}$ mice; the next highest was the $\underline{A}^{y}\underline{a}$ mice. Means for these two genotypic groups are significantly greater than those of the remaining 18 genotypes. All yellow genes at the agouti locus showed no significant effect in lung tumor development. Mean numbers of lung tumors for the yellow mice in the hybrid generations of each C57BL/6 x A/J crosses are not greater than the means of the non-yellow mice, indicating no nonallelic interactions of the yellow genes with the genes conferring susceptibility in the A/J. However, a trimodel distribution of lung tumors showed in the F_2 of the C57BL/6 ($\underline{A}^{iy}$) x A/J, suggesting the presence of a major gene affecting lung tumor susceptibility in the A/J. Since the primary objective of this project was to study the effect of different yellow genes and specific allelic combinations for lung tumor development, it is of interest to note that mice of $\underline{A}^{y}$ in combination with $\underline{A}^{w}$ (the wild type), but not $\underline{A}^{iy}$ or $\underline{A}^{vy}$ mutant), produced duced on the average the greatest greatest number of tumors. The agouti locus, as a complex regulating locus, consists possibly of a number of repeating nucleotide sequences. The yellow genes may represent different deficiences, the $\underline{A}^{y}$ being the most deficient. Under these circumstances, more frequent unequal intragenic crossing over in the $\underline{A}^{y}\underline{A}^{w}$ may occur than in other allelic combinations, thus resulting in more somatic cell mutations. Mutated cells are more susceptible to mutagens or are inferior in repairing ability. As gene regulation in growth and development in eukaryotes is most poorly understood, this interpretation must remain highly speculative. The present results, however, point to the importance of mutation of a regulating locus and possible genetic mechanisms involved in neoplastic development.

Significance to Cancer Research: To determine the role that a gene, or a specific genetic locus, plays in cancer development. The results of this investigation would specifically concern the mutation theory of neoplasm.

Project Officer: Ms. Judith M. Whalen
Program: Immunology Section
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Studies on Macrophage Activation

Principal Investigator: Dr. Emil Skamene
Performing Organization: Montreal General Hospital
City and State: Montreal, Canada

Contract Number: NO1-CB-84269
Starting Date: 9/30/78 Expiration Date: 9/29/81

Goal: Study the interactions of T cells or their products with macrophages that lead to activation of macrophages for reaction against tumor cells.

Approach: Investigate the identity and function of cell populations that control macrophage activation in the development of antilistereal resistance and determine the cellular level of phenotypic expression of genetically controlled high or low levels of antilistereal immunity.

Progress: Detailed autoradiographic studies dealing with the kinetics of monocytopoiesis clearly show that one step being regulated is the cell cycle time (T_G) of promonocyotes, this being significantly shorter in mice of the genetically-resistant (Lr^r) strain. This leads to increased mononuclear phagocyte cellularity not only in the bone marrow, but in every macrophage compartment so far examined. High numbers and decreased life span (T1/2) of monocytes in the circulation of infected (Lr^r) B10.A strain mice are also evident, indicating efficient delivery of macrophage precursors to infective foci. The expression of such a change in monocyte kinetics can be documented well in a model situation of the macrophage inflammatory reaction in response to local irritants, injected intraperitoneally. Linkage analysis on segregating populations has provided the formal evidence that the Lr gene. regulates such macrophage response. Three possible approaches to effect a change from the sensitive to resistant phenotype exist: (a) replacing the animal with the putative Lr^r gene product, (b) elevating the monocytopoiesis of the Lr^s animal experimentally to the level in Lr^r animals, and (c) by-passing the need for prompt macrophage inflammatory response by effective activation of the resident macrophage population. The latter two are being actively examined. Splenectomy proved to be an effective maneuver to enhance the macrophage response in the genetically susceptible Lr^s host, probably by macrophage proliferation in the foci of infection in the liver. Another type of intervention capable of reversing the Lr^s phenotype into the resistant one, was chronic stimulation with BCG. Interestingly, the BCG treatment, although very effective in macrophage activation for listericidal activity in the Lr^s A mice, proved ineffective in correcting the macrophage tumoricidal defect of these animals.

Project Officer: Ms. Judith M. Whalen
Program: Immunology Program
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: International Bone Marrow Transplant Registry

Principal Investigator: Dr. Mortimer Bortin
Performing Organization: Mount Sinai Medical Center
City and State: Milwaukee, WI

Contract Number: NO1-AI/CB-02648
Starting Date: 5/1/80 Expiration Date: 6/30/83

Goal: To aid in improving the success rate of bone marrow transplantation as applied for the treatment of patients with a variety of otherwise incurable diseases including aplastic anemia and hematologic malignancies.

Approach: Maintain a statistical center for the collection, organization and analysis of clinical data provided by transplant teams throughout the world; and disseminate the results of analyses of pooled data to bone marrow teams and to the scientific community.

Progress: Bone marrow transplant teams throughout the world reported detailed data in a uniform fashion to the Resistry at an unprecedented rate during the first year of this Contract. The Statistical Center received and processed reports of 209 new patients. As of April 1, 1981 the Registry had comprehensive data on 864 patients who received 1,022 transplants performed by 60 transplant teams. In addition, 78 follow-up reports were received during the past year. Each new and follow-up report was reviewed carefully and summarized by the Registry staff. When necessary, transplant teams were contacted to obtain missing data for clarification of ambiquities in their reports. Computerization has resulted in an acceleration of the contractor's ability to perform analyses of the data. Detailed reports regarding 215 patients with ALL, ANL, and CML who were treated with supralethal chemoradiotherapy and marrow transplantation between January 1, 1977 and December 31, 1981 have been provided to the Registry by 28 worldwide bone marrow transplant teams.

Significance to Cancer Research: While bone marrow transplantation has now become the treatment of choice for aplastic anemia and selected immune deficiency diseases and very promising results have recently been obtained in acute leukemia in remission, nevertheless a number of complications such as graft-versus-host disease, recurrent leukemia, intercurrent infections and graft rejection remain major problems. The Registry provides the ability to look at the collective experience of many centers, which may facilitate more rapid progress in this form of treatment.

Project Officer: Harriet L.G. Gordon, M.D.
Program: Immunology Section
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Animal Models for Treatment of Minimal Residual Systemic Tumor

Principal Investigator: Dr. Gerald L. Bartlett
Performing Organization: Pennsylvania State University
City and State: Hershey, PA

Contract Number: NO1-CB-33891
Starting Date: 6/30/73 Expiration Date: 10/31/80

Goal: To develop animal tumor models which will be useful for evaluating immune stimulants as immunotherapeutic agents.

Approach: In four different tumor-host models, animals are given immunotherapy at various times after tumor implantation, either alone or in combination with other means of treatment. The effect of the immunotherapy and the role of immune stimulants in immunotherapy are evaluated in terms of improved survival of treated animals. Animals which survive are tested further for improved tumor rejection immunity.

Progress: 13762A Rat Mammary Adenocarcinoma. Rats cured by surgery after day 14 show strong tumor immunity. Concomitant immunity has been used to demonstrate the kinetics of tumor immnity in the treatment protocol employed and to detect immunity-stimulating treatments. Viable tumor cells (10^8) are immunogenic, but irradiated tumor cells are not. In contrast, irradiated tumor cells can evoke DH but mitomycin C-treated cells cannot. Tumor immunity can be adoptively transferred by T-cells.

Line 10 Guinea Pig Hepatoma. L10X, which is an ineffective vaccine in male guinea pigs, is immunogenic for L10 in female guinea pigs that have been sensitized with a male skin graft.

CaD2 Mammary Adenocarcinoma. Treatment with antithymocyte serum abolishes the therapeutic effect of i.t. Cp but not the effect of i.v. Cp. Drug induced tolerance to Cp has been induced. DH tolerance to Cp does not interfere with any of the tumor inhibitory properties of Cp in this model.

LSTRA Mouse Leukemia. Chemoimmunotherapy (CY + vaccine) continues to be inconsistent, even in replicate experiments. Optimal adjuvants and optimal route of injection increase the efficacy of immunity by accelerating the induction of effective resistance to challenge tumor. LSTRA immunity is abolished by either prevaccine or postvaccine treatment with either ATS or CY, or by continuous treatment with trypan blue.

Significance to Cancer Research: These studies demonstrate that caution must be exercised in drawing generalizations on immunotherapy from a single experimental or clinical result.

Project Officer: Harriet L.G. Gordon, M.D.
Program: Immunology Section
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Facility for Supplying Immune-related Cell Lines

Principal Investigator: Dr. Melvin Cohn
Performing Organization: The Salk Institute
City and State: San Diego, CA

Contract Number: NO1-CB-23886
Starting Date: 6/26/72 Expiration Date: 11/30/81

Goal: To supply the scientific community with immune-related lines important in the study of tumor immunology and to increase the library of useful lines as they are characterized.

Approach: Since this is essentially a contract to supply cell lines, little experimental work is involved. However, the general thrust of the laboratory involved the isolation of immune-related lines of the thymus and bone marrow-derived lineages by the use of leukemia viruses, cell fusions, and chemical carcinogens. As new lines become available, they are introduced into the contract catalog.

Progress: The contractor has shipped 973 tissue culture and tumor lines to investigators in the scientific community over the past contract year. The catalog contains detailed characterization of the cell lines. This contract continues to be an excellent research resource increasingly utilized by scientists all over the world. Computerization of inventory and shipments has greatly increased the efficency of the project.

Significance to Cancer Research: The lines in this contract are used by hundreds of laboratories for studies on tumor-specific antigens, antibody structure, immune-related cell functions, somatic genetics, and cell fusions. All of these subjects are major categories under the NCI Cancer Research Program, and the cell lines from this laboratory are key tools in these investigations.

Project Officer: Ms. Judith M. Whalen
Program: Immunology Section
FY 81 Funds: $98,000

CONTRACT RESEARCH SUMMARY

Title: Human Melanoma: Evaluation of BCG Immunotherapy of Patients Without Detectable Disease After Removal of Tumor-containing Lymph Nodes

Principal Investigator: Dr. Donald L. Morton
Performing Organization: University of California
City and State: Los Angeles, CA

Contract Number: NO1-CB-64076
Starting Date: 8/8/74 Expiration Date: 10/7/80

Goal: To determine whether immunotherapy with BCG alone or BCG combined with tumor cell vaccine will decrease recurrence rate or prolong survival in melanoma patients with metastases to regional lymph nodes.

Approach: Patients are randomized following surgical lymphadenectomy into 3 groups receiving different postoperative therapy: one group receives no additional therapy, one receives BCG, and one group receives BCG and allogeneic tumor cell vaccine.

Progress: Recurrences were least frequent in the vaccine treated group (23 out of 47 - 49% compared to 27 out of 46-59% in the control group and 26 out of 45-57% in the BCG treated group). The differences between these recurrence frequencies is not, at present, statistically significant. Patients receiving BCG immunotherapy who recurred are still surviving longer than those in the control group, or those patients receiving BCG plus tumor cell vaccine. A blind analysis of stage II melanoma patients' sera for antibody against M14 did not confirm a previous observation that a modest rise in antibody levels following surgery correlated with a favorable prognosis. However, certain correlations could be made with the disease free interval and survival when absolute levels of antibody were measured in the preoperative period. The mean titer of anti-M14 IgM antibodies was higher in the group of patients remaining tumor free for two years relative to that in patients in whom disease recurred withn two years. A rise of complement fixation antibody titer greater than threefold in patient's receiving BCG with or without tumor cell vaccine was characteristic of patients whose disease did not recur within 30 months of entering the trial. Patients whose disease recurred with 6 to 12 months did not show such a rise in CF antibody titer.

Significance to Cancer Research: It is important to confirm in prospectively randomized trials earlier studies showing immunotherapy to be of benefit to cancer patients.

Project Officer: Harriet L.G. Gordon, M.D.
Program: Immunology Section
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Studies of Immune Stimulants in Patients Receiving Radiation Therapy

Principal Investigator: Dr. William M. Wara
Performing Organization: University of California
City and State: San Francisco, CA

Contract Number: NO1-CB-64004
Starting Date: 6/1/76 Expiration Date: 11/30/80

Goal: To document the immunosuppression which occurs following radiation therapy and to determine if a therapeutic advantage can be achieved by the addition of immunotherapy (thymosin) to the conventional treatment given for squamous cell carcinoma of the head and neck region and the esophagus.

Approach: Both groups of head and neck and esophageal cancer patients will receive radiation therapy and/or surgery as treatment. Patients will then be randomized to receive thymosin or placebo in addition to standard treatment. All patients will be monitored with immunologic tests to measure antibody-mediated and cell-mediated immunity at regular intervals. The data will be analyzed for local disease recurrence, metastatic disease, and survival difference in the patient groups.

Progress: Over 250 controls have been evaluated and their data accumulated to ascertain quality control of the laboratory results. One hundred thirty seven patients have been studied and their preliminary results indicate the expected immunosuppression after irradiation. Following radiation therapy the administration of thymosin did not appear to affect the total number of lymphocytes, total T lymphocytes, and B-lymphocytes. Head and neck cancer patients were normal pre-irradiation with respect to lymphocyte stimulation with PHA. Immediately, post irradiation the thymosin-treated patients showed less suppression than the patients not treated with thymosin, but the values for both groups were suppressed from the pre-irradiation levels. With respect to lymphocyte stimulation by allogeneic cells (MLC), a significant difference is reported between the thymosin treated patients and those not receiving thymosin; the thymosin group retained their MLC capacity after immuno-suppressive irradiation. At three months post irradiation the differences in the PHA and MLC responses between the thymosin-treated and untreated patients became less apparent.

Significance to Cancer Research: This study will determine the significance of immunosuppression caused by irradiation in head and neck and esophageal cancer patients and whether the effect of immunotherapy (thymosin) in reversing this immunosuppression has any impact on disease-free interval, survival, and local control of cancer.

Project Officer: Harriet L.G. Gordon, M.D.
Program: Immunology Section
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Reagents for the Characterization of Human Cell Subpopulations

Principal Investigator: Dr. Marius Teodorescu
Performing Organization: University of Illinois
City and State: Chicago, IL

Contract Number: NO1-CB-84268
Starting Date: 9/30/78 Expiration Date: 9/29/81

Goal: Development of new reagents for the characterizaton of subpopulations of human cells important to the immune response or detection and characterization of new subpopulations of these cells.

Approach: Determine by in vitro tests the function in immune response of lymphocyte subpopulations isolated by specific absorption of human lymphocytes to a bacterial monolayer fixed on a glutaraldehyde-fixed gelatin bed.

Progress: The characterization of the T2 lymphocytes capable of suppressing natural killer cells has been completed. Previous work showed that the T1T2 cells contain precursors for specific cytotoxic lymphocytes. Preliminary experiments demonstrate that the precursors of specifically cytotoxic lymphocytes were exclusively located in T1 lymphocyte subpopulations. Moreover, after the activation of T cells in allogeneic mixed lymphocytes reaction, they maintained the same binding properties for bacteria. After activation, the cytotoxic T cells bind Bacillus globigii. This is particularly interesting since before activation, the cytotoxic lymphocytes do not bind these bacteria. Such results strongly suggest that non-activated specific cytotoxic cells only have the ability of binding Arizona hinshawii and Bacillus globigii. Therefore, it appears that the cytotoxic cells acquire a new receptor, probably a lectin that is identified by bacterial adherence. Additional experiments point out that the T3T4 cells are substantially more efficient in providing help in antibody formation. However, the results obtained so far, cannot establish exactly whether T3 or T4 cells are the actual helpers and additional experiments are underway to clarify these aspects. The identification of lymphocyte subpopulations using both bacteria and monoclonal antibodies suggest that the T1T2 cells are the same cells as those identified by OK-T8 monoclonal antibodies against T cell subsets producted by Ortho Laboratories and the T3T4 cells are the same as those identified by OK-T4. Thus, it appears that the functions that we located in the T1T2 cells and in the T3T4 cells are those shown by others to be performed by cells identified by the OK-T8 and OK-T4 antibodies, respectively. It is noted, that bacteria have substantial advantages over monoclonal antibodies not only from the point of view of cost, but also from the point of view of accuracy, accessibility of morphology, simplicity etc.

Project Officer: Ms. Judith M. Whalen
Program: Immunology Section
FY 81 Funds:

CONTRACT RESEARCH SUMMARY

Title: Immunologic Mechanisms of Cattle

Principal Investigator: Dr. Charles Muscoplat
Performing Organization: University of Minnesota
City and State: St. Paul, MN

Contract Number: NO1-CB-84244
Starting Date: 9/30/78 Expiration Date: 9/29/81

Goal: Perform in vitro studies of immunologic mechanisms in cattle in conjunction with ongoing immunoprophylaxis studies to gain information on the possible influence of immunity on carcinogenesis.

Approach: Perform in vitro studies on the cellular and humoral events of the bovine immune system on tissues provided by NCI from experimental animals involved in a study of immunoprophylaxis of bovine ocular squamous cell carcinoma to determine whether correlative changes in immune response can be detected during the process of cancer development and, if so, to determine the immunologic mechanisms involved.

Progress: A sensitive radioimmunoassay has been developed to detect antibodies against cell surface antigens on bovine ocular squamous cell carcinoma lines. Results show that most (if not all) animals with tumors possess antibodies to their own tumor cells as well as allogeneic tumors. Differences in reactivity between autologous and allogeneic reactivity as yet cannot be determined. Normal cattle sera are non-reactive against all tumor cell lines as are tumorous cattle against normal corneal cell lines. These studies clearly indicate that it is easy to detect serum containing antibodies to tumor cells but difficult to distinguish one animal's tumor from another. Furthermore, in several instances the examination of plaques and papillomas which have originated from the same animal has not been able to distinguish them from one another using radioimmunoassay. Absorption experiments designed to determine cross reactivity of these antibodies show that all the tumor cells examined to date have a similar antigenic make up because all cells will absorb out antibodies to other cells (excluding normal controls). In studies involving natural cytotoxicity lymphocytes from normal and tumor bearing cattle have been examined to determine if lines derived from bovine ocular squamous cell carcinoma could be assayed for killing. Moderate levels of killing of several of these cell lines were observed. However, the degree of cytotoxicity varies with the passage of tumor cells in culture. It is not yet possible to detect differences in the lysis of tumor cells from different stages of tumor growth using natural cytotoxicity.

Project Officer: Ms. Judith Whalen
Program: Immunology Section
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Reagents for the Characterization of Human Cell Subpopulations

Principal Investigator: Dr. Noel Warner
Performing Organization: University of New Mexico
City and State: Albuquerque, NM

Contract Number: NO1-CB-84288
Starting Date: 9/30/78 Expiration Date: 9/29/81

Goal: Development of new reagents for the characterization of subpopulations of human cells important to the immune response of detection and characterization of new subpopulations of these cells.

Approach: Develop specific heteroantisera against defined populations of human lymphoid cells stressing nonmalignant populations, including T_{γ}, T_{μ} and T null cells, and other T cell preparations, as well as B cell populations defined by various available cell surface markers, and macrophage subpopulations.

Progress: This study is intended to characterize the subset of human peripheral blood cells which bind to the Fc portion of human IgG (previously referred to T_{γ} cells) and to develop reagents that are exquisitely specific for these cells. Studies have demonstrated that this subset of cells expresses an Fc receptor that is capable of binding to monomeric human IgG of either myeloma or normal type, and thus by that criterion would be analogous to the Fc receptors so far identified only on macrophage lineage cells. Using a series of monoclonal antibodies from commercial sources it has also been demonstrated that these cells lack OKT3 and other T cell specific antigens, but do express the OKM1 antigens predominantly expressed on cells of the monocytic lineage. It is thus concluded that the majority of so-called T_{γ} cells are cells in the monocyte macrophage lineage. Using flow analysis the light scatter properties of these cells form in a relatively restricted medium scatter range distribution. Present studies are now in progress to develop monoclonal antibodies against these cells. These cells mediate natural killer activity on a range of human tumor target cells. These studies thus suggest that the monoclonal antibody raised against these cells might have the specific ability to inactivate natural killer function or to monitor for NK function in a variety of human tumor target cells. In other studies a series of hybridoma fusions have been performed and are in varying stages of cloning, characterization and further development.

Significance to Cancer Research: The development of reagents for characterizing subpopulations of human cells important to the immune response may facilitate analyses and manipulation of the immune response to human tumors.

Project Officer: Ms. Judith M. Whalen
Program: Immunology Section
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Selective Depletion of Mononuclear Phagocytes In Vivo

Principal Investigator: Dr. Stephen Russell
Performing Organization: University of North Carolina
City and State: Chapel Hill, NC

Contract Number: NO1-CB-84271
Starting Date: 9/30/78 Expiration Date: 5/1/81

Goal: Development of methods for the selective in vivo destruction or sustained functional inactivation of mononuclear phagocytes.

Approach: Produce specific antimononuclear phagocyte globulin by selective absorption and assess the effect of these reagents on mononuclear phagocytes in vivo using "immune" granuloma formation in presensitized mice and spontaneous regression of Moloney Sarcomas in mice as model systems.

Progress: As was previously shown, the major cross-reactivity in the anti-bone marrow serum was to neutrophils. Therefore it was necessary to find the means to obtain large numbers of neutrophils free of mononuclear phagocytes. Perironeal exudate cells collected 1, 2.5 or 4 hours after the intraperitoneal injection of 1 ng LPS proved to be a rich source of neutrophils. The neutrophils were found in the cell pellets with greater than 95% purity and only 1-3% contamination with mononuclear phagocytes. The contamination with mononuclear phagocytes was found to be caused by liquid from upper layers mixing with the cell pellet. By pouring off the supernate and washing the sides of the inverted tube, the mononuclear phagocyte contamination was reduced to less than 0.5%. The number of neutrophils required to eliminate the anti-neutrophil activity of the anti-bone marrow IgG fraction was determined by titration. This laboratory has become increasingly aware of the potent effects of endotoxin on mononuclear phagocytes and, therefore, determined if endotoxin would affect their depletion assay. It was determined that 1000 ng/ml had a profound effect on the influx of mononuclear phagocytes into the peritoneal cavity after PHA stimulation. However, even 50 ng/ml had a depressive effect on the influx of mononuclear phagocytes when compared to PBS controls.

Significance to Cancer Research: Studies on the in vivo depletion of macrophages will aid in examining the roles of macrophages in tumor destruction.

Project Officer: Ms. Judith M. Whalen
Program: Immunology Section
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Immunoprophylaxis of Bovine Lymphosarcoma

Principal Investigator:	Dr. Richard M. Thorn
Performing Organization:	University of Pennsylvania
City and State:	Philadelphia, PA
Contract Number: NO1-CB-84243	
Starting Date: 9/30/78	Expiration Date: 9/29/81

Goal : Study the immunoprophylaxis of bovine lymphosarcoma through administration of BCG cell wall vaccine by intravenous injection as a possible guide for the control of analogous human disease.

Approach: Study the effect of the administration of BCG cell wall vaccine on the extent and rate of development of lymphosarcoma in cattle injected with bovine leukemia virus at a stage prior to the development of discernible evidence of disease.

Progress: One of the unusual immunologic phenomena associated with BLV-infected cattle is that their peripheral blood leukocytes spontaneously incorporate thymidine in vitro. In this reporting period a systematic evaluation of the conditions for generating spontaneous blastogenic activity has been completed. The group demonstrated that only lymphocytes from BLV-infected cattle have a spontaneous blastogenesis which is inhibited by BLV antibody. Conditions have been standardized for the measurement of putative bovine T cells, which as judged by the literature, has been difficult. Of the 10 cattle in this study which have died, 6 are known to have had lymphosarcoma. Since 3 were BCG treated and 3 were not, it appears that BCG did not have pronounced inhibitory effect. The number of cases is too small to evalulate the effect of BCG on the rate of deaths associated with lymphosarcoma. The 2 cattle whose lymphosarcoma status at death is not yet known were BCG-treated. At present there is no evidence, therefore, that BCG-CWS given twice intravenously reduces the incidence of naturally occurring, BLV-associated lymphosarcoma. Other studies imply that BLV infection induces a lymphocyte population which undergoes spontaneous blastogenesis in spontaneous DNA synthesis has been demonstrated in cultures of antigen specificity. This is, then, the first demonstration of specificity in a "spontaneous" immune response. This phenomenon may be unique to cattle and BLV infection or it may be a more general immunologic property which is easily detected in BLV-infected cattle because of the chronic nature of BLV infection. Plans are underway to determine the cellular basis and function of the inhibitable 3STI activity found in lymphocytes from BLV-infected cattle.

Project Officer: Ms. Judith Whalen
Program: Immunology Section
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Immunoprophylaxis of Cancer Eye in Cattle

Principal Investigator: Dr. Stephen J. Kleinschuster
Performing Organiztion: Utah State University
City and State: Logan, UT

Contract Number: NO1-CB-74155
Starting Date: 9/16/77 Expiration Date: 12/15/80

Goal: To develop immunologic maneuvers for interfering with the progression of solid tumors from the premalignant (benign) to the malignant state. To relate the immunologic status of experimental animals to clinical events.

Approach: Intralesional administration will be made of BCG cell wall vaccine into benign ocular lesions of cattle to determine whether such treatment will retard or prevent the normal progression of these lesions to the malignant state. Additionally, the immunologic status of animals will be monitored.

Progress: The data shows, in general, that there were more regressed lesions in the active vaccine group than the others; however the significance level was variable. There were also fewer progressive lesions and malignant transformations in the active vaccine group than the others (high levels of significance). Thus, active vaccine administered intralesionally can interrupt th transformation process and is a true prophylactic treatment. The collection and cryopreservation of tumor tissue and blood components was completed. Surgically removed tumor tissue has been frozen in saline (90° C). Bovine red cells are resistant to insult and can be frozen without elaborate preparation. Bovine lymphocytes and monocytes, however, are much more fragile than their human counterparts. A protocol was developed for the successful cryopreservation of bovine lymphocytes with a resultant 90% or greater viability upon thawing. Dr. C.C. Muscoplat has been supplied with all the blood components he will need for his analyses of immunocompetence of the experimental animals. Additionally, he has been supplied with approximately 35 cell lines from various animals in this study using techniques developed in the laboratory. These lines are from all stages of the malignancy including normal, plaque, papilloma and frank carcinoma.

Significance to Cancer Research: Studies involving the immunologic interruption of the transformation of a benign precursor lesion to one of malignancy at the earliest possible stage provide valuable contributions to the overall cancer effort. Additionally, via a program of monitoring the immunocompetence of experimental animals as related to clinical events following experimentation, relevant information can be contributed to the establishment of effective immunologic testing needed in order to evaluate therapy and provide guidelines for improved human clinical protocols.

Project Officer: Ms. Judith Whalen
Program: Immunology Section
FY 81 Funds: 0

BREAST CANCER PROGRAM COORDINATING BRANCH

October 1, 1980 - September 30, 1981

Description

The objectives of this extramural Program are to promote and support multi-disciplinary research projects in the laboratory and in the clinic that will lead to improved methods of diagnosis, prognosis, treatment and prevention of breast cancer. These objectives are accomplished through the collaborative activities of the staff of the Branch and the members of the Breast Cancer Task Force Committee, an extramural advisory group. The members of the Task Force suggest new and innovative research ideas based on their knowledge of ongoing research in breast cancer as well as drawing upon their own expertise in the field; and information obtained at workshops and conferences in which the state-of-the-art on specific topics is presented. The staff of the Branch organizes the ideas into requests for investigator-initiated applications (RFAs) or Program Announcements (PAs), or requests for contract proposals (RFPs) depending upon the mechanism of funding considered most advantageous to achieve the goals of the project.

The Branch is organized into four program areas or Sections, namely, Diagnosis, Epidemiology, Experimental Biology and Therapeutics, with a fifth section on Information. The grants and contracts managed by each of the four Sections have been categorized by scientific relevance and are presented at the end of this summary.

Accomplishments

The grants program in breast cancer has increased in scope, in number, and in funding. In the previous fiscal year 46 grants for a total of approximately $5 million dollars made up the program and in this year the number has increased to 88 for a total of almost $10 million. The extent of the present program is shown in tabular form.

Both the Diagnosis and the Epidemiology areas have increased the scope of their programs with grants received in response to RFAs and Program Announcements. The Diagnosis area funded three grants from seven applications received in response to a Program Announcement on research related to problems on mammographic screening. Each of the three projects initiated has a different approach to studying the effects of radiation on mammary tissue or cells. The RFA in this area was related to studies of immunocompetent cells infiltrating human breast cancer, two of seven applications were funded. In the Epidemiology area the Program Announcement on genetic susceptibility to human breast cancer has been productive of applications, a total of nine, however, no awards have been made. The RFA on correlation between microscopic characteristics of primary breast tumors and subsequent patient survival resulted in receipt of 17 applications. Four of these received excellent scores however the funds set aside for the RFA permitted only the initiation of two grants. All four applications represented different scientific approaches to the problem therefore it would have been

Breast Cancer Research Program
Fiscal Year 1981

Project Category	Grants		Contracts	
	Number	Funds	Number	Funds
Experimental Biology	48	$4,859,841	10	$ 148,500
Epidemiology	11	2,003,258	14	274,000[a]
Diagnosis	14	1,441,921	10	27,000
Treatment	15	1,593,646	17	783,918[b]
Totals	88	$9,898,666	51[c]	$1,233,418
Grand Totals - Grants and Contracts	139		$11,132,084	

a $80,000 Provided by the Nutrition Program, NCI
b $105,073 Provided by the Office of the Director, NIH
c 19 Contracts Received Funds

highly desirable to have funded each. The applications to the two Program Announcements were reviewed by regular Study Sections while those to the RFAs were reviewed by Special Study Sections.

Although the Experimental Biology and Treatment areas have not advertised new projects each has increased their program. Some of the new grants funded in the four areas can be attributed to the encouragement of investigators by staff of the respective Sections to apply for support for new and relevant breast cancer projects. Both in the areas of Experimental Biology and Diagnosis, research related to the production and characterization of monoclonal antibodies for breast cancer has received initial support.

The grants of the total program include: 79 ROls-Regular Grants, competitive and renewals; 2 POls-Program Project Grants, one basic research, one clinical; 5 R23s-New Investigator Awards; and, 2 R23s-Conference Grants.

Projects funded by contracts have continued to decline, in the previous fiscal year there were 80 funded for a total of $3.1 million; this year (FY 1981), there were 51 however only 19 received funds, a total of $1.2 million. Those not funded but continuing were either completing their final year or received extensions without additional dollars, the majority of the remaining contracts are follow-up of clinical studies. The two contracts that received the most dollars are service in nature.

The Task Force Committee membership has been reduced from 38 to 27 members in Fiscal Year 1981. On several occasions it has been necessary to invite one or more ad hoc investigators for a meeting in order to have expertise that was lacking within the present membership. The Committee has met four times during the year and at each of the first three meetings one half-day was devoted to a workshop or scientific session, at the last meeting a full day workshop was held. Topics for the workshops have been suggested by members of the Committee and in some instances members have presented their own work. The topics and sponsoring Program areas were: 1. "Luteal Phase Defects and Breast Cancer Risk" - Epidemiology. 2. "Clonogenic Assays and Chemotherapy Sensitivity" - Treatment. 3. "Chemical Carcinogen-Hormone Interaction in Transformation of Mammary Epithelial Cells In Vitro" - Biology. 4. "Monoclonal Antibodies in Breast Cancer" - Diagnosis. Additionally the Epidemiology Program area in collaboration with the Diet, Nutrition and Cancer Program, NCI, sponsored a day working session on "Diet and Breast Cancer Risk;" and, it was also responsible for bringing three speakers to present their work on "Specific Dietary Factors in Relation to Benign Breast Disease or Cancer." The specific topics were: abstenance from intake of methylxanthines, coffee, tea, colas, and chocolates; Vitamin E (tocopherol) supplement to diet; and a literature review on studies of Vitamin A and cancer. Attendance at these meetings has been excellent, Task Force members, NCI and other NIH staff, basic and clinical investigators from universities and other research organizations in this country and abroad, pharmaceutical organizations and lay persons have attended. Only Task Force members and invited speakers have been reimbursed for participation. The purpose of a workshop is to review the state-of-the-art and to determine the need for promoting new research. Members of the staff of the Branch have been preparing projects to be advertised for RFAs, Program

Announcements and RFPs resulting from suggestions made at the time of each workshop. All projects must be approved by the DCBD Steering Committee and the DCBD Board of Scientific Counselors before they are published. Because of the time of the meetings of the Board no new projects have been published in this fiscal year.

In the coming year the following research projects and others will receive emphasis from the staff and advisors: monoclonal antibodies, diagnosis and treatment; new diagnostic methods, particularly diaphanography and NMR; improved techniques for clonogenic assays; specific dietary factors in relation to benign breast disease and cancer; genetic markers in high risk families; identification of intravascular tumor growth in histological sections; and, luteal phase defects and breast cancer risk.

Diagnosis Section

The Section continues to be concerned with major clinical issues that confront the physician in the diagnosis and prognosis of breast cancer. These issues encompass several medical disciplines and include such problems as early diagnosis, separation of non-neoplastic from early neoplastic conditions, staging, determinants of biological behavior and predicting prognosis and recurrence. The section has supported through grants and contracts basic and applied research related to these issues. Although some may feel that progress is slow, we confidently believe that definite advances have been made. Studies on breast cancer are complicated by the nature of the lesion and by the many endocrine and other factors that affect breast tissue. The following describes different projects which we have developed to address these issues:

Biological Markers:

Efforts to identify biological markers continue to receive special attention. The importance of markers lies in their many potential uses. For instance, they might detect incipient cancer, confirm a clinical diagnosis, or stage a patient for therapy. They may prove useful in estimating prognosis and predicting recurrences. Currently, the three most useful markers are ferritin, calcitonin and CEA. Unfortunately, these are not reliable for early detection and cannot always be used to predict prognosis. The Section has awarded one grant and six contracts in its search for biological markers. One of our objectives in marker research (NO1-CB-84222) is to quantitate and characterize the different isozyme patterns in normal, benign and neoplastic breast tissue. Although the isozyme patterns of normal and malignant tissues are known to differ, we would like to take advantage of this difference to find serum or tissue enzymes that reflect the presence of cancer. Of 23 different isozymes tested only three seem promising: lactic dehydrogenase, malic acid of dehydrogenase and esterase. Because these isozymes exist in tissues, they can be detected by histochemical methods, which might prove helpful to the pathologist for differentiating borderline lesions.

In another study (CA25574) the isozyme differences and the effects of mammotropic hormones on these differences are being investigated.

Concerning prognosis, the Section has supported longitudinal studies (CB-74086 and CB-74206) in breast cancer patients to learn if long-term changes in the levels of serum enzymes or other constituents can be used to predict recurrence. Although time consuming, these types of studies are especially valuable. Based on information from the initial presurgical and surgical blood data, a complex multi-variate model has been developed that will now be tested in a prospective study. Based on the recurrent patterns of patients followed for a period of time, this model successfully predicted nearly 80% of recurrences. It should be noted, however, that the relationship of putative serum markers to recurrence is not always clear. For instance, in some patients with metastatic breast cancer, elevation in markers preceded the clinical metastasis while in other patients no changes occurred. In addition to correlating changes in the serum levels with time, investigators are also exploring the relationship between marker concentration in tumor tissue and its level in the blood.

In addition to malignant diseases, we have turned to benign breast diseases in an effort to identify new markers, especially those that may correlate with the subsequent development of cancer. Contract CB-53853 has analyzed fluid aspirated from benign mammary cysts. Results from over 1600 samples showed that CEA, alpha-fetoprotein, the beta subunit of human chorionic gonadotropin, calcium and other metals, cholesterol, numerous enzymes, steroids and cell breakdwon products are present in the cystic fluid in much higher concentration than in serum. These patients are now being followed to establish whether the development of cancer, which is expected to occur in a certain number, will correlate with the initial biochemical findings. These types of studies are extremely time consuming, but they are considered very useful.

Other research projects (CB-84223 and CB-84316) have been concerned with distinguishing premalignant hyperplasia from non-premalignant hyperplasia. These studies involved the extensive use of biochemical, morphologic and immunologic techniques in order to associate putative markers in tissues with malignancy. They should have practical significance if specific markers can be identified that are easily measured on routine histologic sections. Results from these projects have shown that CEA is present in malignant lesions and in severe epithelial dysplasia, but only rarely in cases of fibrocystic disease. IgG has been found in a pericellular pattern in dysplasia while IgA predominates in non-dysplastic benign lesions. The presence of IgG seems to correlate with lymphopenia. The full significance of these remains to be established. Angiogenic factor, which stimulates vascularization, has been found in a large number of atypical breast lobules obtained from women with carcinoma and in a smaller number of atypical lobules obtained from women without cancer.

Methods of Detection:

Regarding non-invasive methods of detection, two grants have been initiated. One (CA25836) is designed to test the feasibility of localizing breast lesions by gamma imaging techniques using radiolabeled steroidal and other derivatives that bind specifically to estrogen receptors. A number of gamma

labeled iodostilbestrol and halogenated hexestrols that bind to these receptors have been synthesized and characterized. These compounds are presently undergoing in vitro and in vivo testing.

Studies on diaphanography and nuclear magnetic resonance have been investigated and will receive more attention in the coming year.

One study (CA28967-01) was recently funded in which a scanning electron microscope is used to magnify the images of microcalcification obtained by low dose mammography. The purpose of this investigation is to determine if early granular calcification indicates the presence of cancer even before its pattern can be discerned on routine film examination by the radiologist. Although it is impractical to use a scanning electron microscope routinely, the results of this study should tell us if the pattern of microcalcification is established early in the evolution of neoplasia and if it can be used for early diagnosis.

Another long-term concern has been adverse effects of diagnostic modalities. For instance, three grants (CA29940, CA29993, CA29781) in response to a Program Announcement were recently awarded to study the effects of irradiation on mammary carcinogenesis in rats and DNA damage repair in mammary cells.

Morphologic Discriminants:

Accurate diagnosis and morphologic assessment of breast cancer remains a challenging problem for the Section. The statistics regarding the incidence of breast cancer indicate the need for early and effective diagnostic evaluation. Interest in early evaluation includes an assessment of the probability of invasive cancer following hyperplasia or in situ cancer as well as in histologic markers for the separation of borderline lesions.

In order to ascertain the risk of invasive cancer with in situ and dysplastic lesions, we have been supporting a histologic review (CB-74098) of a large number of carefully followed women with an initial diagnosis of in situ carcinoma, atypical hyperplasia or other benign conditions. This work is of practical importance because it may improve diagnostic criteria pathologists use to estimate the biologic behavior of these lesions. The histologic evaluation of dysplastic and other atypical lesions has been controversial for years.

Studies to define whether expression of common blood group antigens, such as the ABO system and T-antigen, on the primary cancer can be used to predict metastatic spread (CA28128). It is also possible that these blood group antigens may also be useful in differentiating hyperplasia from early malignancy. Results with the T-antigen indicate that the pattern of intracellular distribution may be important. T-antigen was found only along the apical cytoplasmic membrane in 19 of 22 benign breast lesions whereas a diffuse cytoplasmic distribution was seen in 17 of 22 cases of breast cancer. The carcinomas which did not display the T-antigen were the most poorly differentiated of the group.

A marker (CA26406) has been found that differentiates mammary epithelial cells from mesenchymal cells and from myoepithelial cells. This marker should separate lesions originating from ductal or lobular cells as opposed to those arising from myoepithelium. The marker is actually keratin, which occurs in small amounts in epithelium.

Immunodiagnosis:

The potential clinical use of immunological methods for diagnosis and for estimating prognosis is a critical concern. There are four grants and two contracts relating to immunodiagnosis in breast cancer. Although in the past studies were usually directed at correlating prognosis with the extent of the inflammatory response to the tumor, more recent studies have been toward measuring the functional ability of these lymphocytes. For example, contract CB-84228, has been assessing the prognostic significance of the cell-mediated immune reactivity in standarized in vitro tests. The results firmly suggest that the tumor does affect functional activity in regional lymph nodes, an observation that may have bearing on the metastatic potential of breast cancer. This field should continue to attract considerable research interest for there is little information concerning the function of intratumor leukocytes and their relation to any immune response. In this regard, we have recently awarded two grants (CA29601, CA29586) to investigate immunocompetent cells that infiltrate human breast cancer.

In addition, research designed to correlate the level of circulating antigen-antibody complexes with prognosis, estrogen receptor levels and other variables (CB-84224 and CA25653) has been supported. Circulating immune complexes are found in many patients with cancer including those with breast cancer. Following an analysis of over 400 patients, immune complexes measured by several different techniques have been found in nearly all breast cancer patients and in some patients with benign breast disease. As expected, the levels of these immune complexes have varied with the different methods used. According to preliminary analysis, the level correlates with the estrogen receptor content of the tumor and certain risk factors. Patients with Stage 2 have higher levels than patients with Stage 1 disease. Levels do not correlate with circulating CEA levels. The results also indicate that the Raji assay is most effective in differentiating cancer from non-cancer groups.

The levels of immune complexes vary depending on past history, especially in patient with a history of genital urinary tract infection or hypertension. These latter observations are not only important for breast cancer patients, but for all cancer patients. One study that remains to be done is to determine the nature of the antigen that forms the immune complex. In addition to evaluating the level of immune complexes in breast cancer patients, the investigators are improving the techniques for measuring these complexes.

Also skin tests are being evaluated as a possible diagnostic tool (CA19083). There is evidence that the Thomasen Frendenreich (T) antigen which is a carbohydrate precursor antigen for the MN blood group system is specifically associated with adenocarcinomas of the breast. Preliminary data indicate

that breast cancer patients and a small number of patients with benign disease show both humoral and cell-mediated immune reaction to the T-antigen. As part of a prospective study, these antigens are being measured in patients without known breast cancer and in patients who will have a breast biopsy for suspected malignancy.

Other Activities:

In collaboration with the College of American Pathologists, the Section organized a symposium on "The Management Assessment of the Aspiration Needle Biopsy in Breast Cancer," which was held in San Diego during the spring meeting of the College.

Workshop on "Monoclonal Antibodies in Breast Cancer."

Epidemiology Section

Fourteen contracts and eleven grants are categorized under nine different areas of focus in our epidemiologic studies of breast cancer. Five of these represent more than one category, since the categories are intertwined; one of these five (CA13556) is a program project grant with a broad, mulit-disciplinary approach to the etiology, epidemiology, and natural history of breast cancer. Seven of the fourteen contracts (CB-53884, CB-53968, CB-63996, CB-63997, CB-74102, CB-74103, CB-74104) terminated in Fiscal Year 1981; one of the other seven ongoing contracts was extended without funds. Eight new grants have been added to the program this year; two of these were top-scoring responses to a specific RFA.

In the area of genetic susceptibility to breast cancer, one grant (CA27632), following up our previous contract-funded research by this same investigator, is extending research stemming from her very important discovery that breast cancer susceptibility appears to be linked, in some but not in all breast cancer prone families, to the locus for glutamine pyruvate transaminase (GRP-1), a marker gene provisionally located on chromosome 10. This strong evidence for at least one gene for breast cancer susceptibility is a major breakthrough that has opened up an entire new realm of research, including their continuing attempt to localize other genes for susceptibility through similar linkage analysis, as well as the search for the phenotypic expression of such a gene. A related grant (CA30069) is exploring hormone metabolism patterns associated with familial high risk.

The endocrinology of breast cancer etiology has continued to be explored through a variety of studies: A. Examining exogenous estrogens as a risk factor (CB-53884, CB-74099). B. Seeking differences between pre- and postmenopausal breast cancer (CB-63996). C. Defining endocrine events at the time of first pregnancy in young and in older women (CB-74101). D. Exploring epidemiologic risk factors in relation to steroid hormone receptors and hormone binding globulin (CA13556, CB-63996), and examining these in relation to prognosis (CA28720). E. Studying hormone metabolism associated with familial breast cancer (CA30069). F. Searching for possible relationships between breast cancer and prior thyroid diseases (CB-84230).

Interaction with pathology has involved explorations of possible differences in the epidemiology of different histopathological subcategories of breast cancer (CB-53968, CB-63997).

Program interest in the natural history of breast cancer has led to studies on the epidemiology of benign breast disease(s), (CB-74102, CB-74202, (CB-84231, CA13556, CA26021, CA28720) and of minimal breast cancer (CB-74103). A particular focus is the epidemiology of benign lesions most prone to progress to breast cancer. Incidence of benign breast disease is also being examined in ethnic subsets of the population known to differ in their risk of breast cancer (CB-84231). In relation to natural history, a mathematical two-hit model was developed for the pathogenesis of breast cancer; this model was in good agreement with available incidence and epidemiologic data (CB-74100, completed in Fiscal Year 1980).

Concern about environmental risk factors has continued; attention has been focused not only on exogenous steroid hormones, but also on other possible carcinogens, and particularly on the possible role of diet (CB-53884, CB-74104, CB-84229, CB-84318; CA30273, CA30629). Special emphasis on cholesterol and lipids has been timely in terms of present interest in a possible negative correlation between risk for cardiovascular disease and risk for cancer. The principal finding in terminated contracts CB-84238 and CB-84317 (terminated in Fiscal Year 1980) was that there was no relationship between prior serum cholesterol level and the subsequent risk of development of breast cancer. Another ongoing contract (CB-84318) is continuing to explore differences between breast cancer cases and controls. Emphasis has been placed on possible mechanisms and rationale for a dietary effect. The effect of obesity and of weight loss on steroid hormone metabolism is being determined (CB-84229). Significant differences have been found between vegetarians and omnivores in the excretion of estrogens and the metabolism of steroids by the intestinal flora (CB-74104). Dietary fat is being examined in relation to physical chemical properties of the cell membrane, immune responsiveness, and tumor cell susceptibility to cytotoxicity (CA30273, CA30629). Carcinogens and mutagens that may particularly impinge on breast ductal epithelium are being determined from examination of breast fluids (CA13556).

Interest has also focussed on risk factors of possible relevance to tumor agressiveness and hence to prognosis; new stuides are aimed at exploring specifics of epidemiology and of the morphology, biochemistry, immunology, and immunohistochemistry of breast tumors in relation to prognosis and survival (CA28720, CA30335, CA30342). These will include attention to antiviral antigens in relation to breast cancer risk and to prognosis of breast cancer (CA29711, CA30342).

The overall emphasis of the Epidemiology Program is not simply statistical, descriptive epidemiology, but rather a broad, multidisciplinary approach to the exploration of possible etiologic mechanisms and the risk factors influencing these. Program has maintained a continuing relationship with the Diet, Nutrition, and Cancer Program (DNCP). The Section Chief serves as a member of the NCI Nutrition Working Group, and represents the Division of Cancer Biology and Diagnosis on that group. In this capacity, she has

participated in the discussions and decisions on policies and recommendations regarding NCI funded nutrition research, and in their interaction with the Nutrition Subcommittee of the National Cancer Advisory Board. As mentioned early in this report the Epidemiology Section and DNCP cosponsored a Working Session on "Diet in Relation to Breast Cancer Risk" in April 1981 that attracted a large attendance and valuable discussion on future avenues of research in the area.

Experimental Biology Section

The program maintains the largest number of investigator-initiated research projects that encompass a variety of scientific approaches to basic biology. Five contracts were terminated in Fiscal Year 1981 (CB-74094, CB-74188, CB-84134, CB-84225 and CB-84239) and contract (CB-74175) continues to serve as an animal tumor and human breast cancer cell culture bank. Contracts (CB-84134 and CB-84225) are service oriented for the production of antibodies to various types of collagen and the carboxyterminal non-helical sequences of human Type I procollagen. Contracts (CB-74094 and CB-74188) are research oriented to determine factors for growth and passage of normal mammary epithelial cells in culture. The largest number of grants were assigned to the Section resulting in a larger number of funded grants. There were 48 grants in the program in Fiscal Year 1981 that are competitive and non-competitive, one Program Project, three New Investigator Awards and one Conference Grant.

The funded grants conduct research relating to various categories such as: I) Factors in the Induction of Mammary Tumors (CA18946, CA27026, CA27293, CA20764, CA18664, CA25915, CA31207, CA21993, CA22879, CA28999, CA30036, CA31774 and CA30570); II) Growth Passage and Characterization of Normal Mammary Epithelial Cells (CA05388, CA24844, CA29090, CB-74094 and CB-74188); III) Mammary Tumor Response to and Dependence on Hormones (CA16660, CA21606, CA20605, CA30171, CA26869, CA18664, CA27293, CA28645, CA28698, CA28393, CA18458, CA16464, CA22343, CA24687 and CA29501); IV) Interaction of Neoplastic Mammary Cells With Other Cell Populations (CA25179, CA20764, (CA20122, CA28366 and CB-84239); V) Cell Surface Proteins in Relation to Metastasis (CA19814, CA27909, CA31695, CA19455, CA08418, CA27314, CA26825, CA25418 and CA28844); VI) Prevention of Neoplastic Transformation (CA30036, CB-74207); VII) Pathophysiology of the Solid Mammary Carcinoma and its Relation to Metastasis (CA05388, CA29537 and CA28735); VIII) Immunodiagnosis and Immunoprevention of Cancer Growth and Progression (CA27437, CA30284 and CA20286); IX) Service, Support and Resource (CB-74175, CB-84225, CB-84314, CA28816 and CA30294). Because of the types of research grants some were included in two or more categories as CA05388 in categories II and VII; CA18644 and CA27293 in categories I and III; CA20764 in categories I and IV; CA30036 in categories I and VI. A research summary on each contract that includes information on goals, approaches and progress, as well as, a list of the grantees' institutions, principal investigator, grant numbers and titles of the research projects appends this report.

A Workshop entitled "Chemical Carcinogen-Hormone Interaction in Transformation of Mammary Epithelial Cells In Vitro" was sponsored in April 1981. Six investigators with expertise in this scientific area were invited to

present their latest research. The workshop was very successful and the concensus was that epithelial cell culture techniques and research methods are available to study the epithelial transformation process which hitherto was done with fibroblasts.

Therapeutic Section

This program is primarily concerned with developing new knowledge about tumor biology which can be applied to the optimal selection and utilization of various treatment modalities.

Fifteen contracts and fifteen grants are listed under five major research areas. In addition, the data management center constitutes a resource contract (CB-14339). Five contracts were terminated in Fiscal Year 1981 (CB-33899, CB-43917, CB-74137, CB-74140 and CB-84221) and four were confined to clinical follow-up observations.

For more than a decade the program has been deeply involved with steroid receptor technology and interpretation as a means of predicting hormone dependency of breast cancer tissue. Three grant supported studies (CA22828, CA26452 and CA27470) are directed toward elucidating the physiologic activity of the steroid receptors. With the trend toward receptor assays being performed on all patients with primary and metastatic breast cancer, there is need for procedures that are simpler and more reproducible than the standard methods. There also is need for methods that will demonstrate the histologic distribution of the receptor proteins. One grant supported project (CA29971) and two contracts (CB-23862 and CB-43969) have these objectives. An evaluation-oriented contract (CB-04388) funded from the Office of the Director, NIH, is sampling the impact on clinical management of breast cancer produced by the application of steroid receptor data.

The search for biological markers in breast cancer patients continues. Four contracts (CB-74137, CB-74138, CB-74213 and CB-84296 are resource oriented with the aim of establishing a bank of serum specimens from which qualified investigators may draw panels of coded specimens to test their purported markers. Three medical centers are processing serum samples from 1) asymptomatic women, 2) women with benign breast disease and 3) patients with breast cancer. The samples are stored in a Mayo Foundation facility where they are coded and held for distribution to the investigators.

Research studies in the biomarker area are being carried out by one grantee and two contractors (CA26935, CB-43900 and CB-74204). Dr. Tormey is testing CEA and FHAP as breast cancer management parimeters, Dr. Dao is studying sulfotransferase enzymes as clinical prognostic markers and Dr. Hilf is measuring a panel of tumor isoenzymes as potential prognosticators of response to chemotherapy.

A group of seven grant supported projects and one contract (CA02071, CA05197, CA23079, CA24129, CA25586, CA26004, CA30251 and CB-84221) deals with the mechanisms by which chemical and endocrine treatments cause alterations in breast tumor growth. They explore specific tumor, host or

treatment factors such as cytokinetics, immunological parameters, endocrine profiles during cytotoxic therapy, and intratumor steroid metabolism.

Animal models for preclinical treatment testing are the major thrust for two grant studies (CA26287 and CA29006); a rat mammary carcinoma system for c. parvum and canine breast cancers for envelope glycoprotein 55.

The final category is clinical investigation with five contracts and one grant (CB-33899, CB-43917, CB-43990, CB-53851, CB-53917 and CA30006). Four of the contract-supported studies are involved with systemic therapy, adjuvant to local therapy, for patients with tumor localized to the breast and axillary nodes. The fifth tests endocrine suppressive therapy against advanced breast cancer. The adjuvant studies have completed patient accrual and the courses of treatment and are in the long-term follow-up phase. The advanced breast cancer project has also finished patient enrollment but continues with in depth endocrine studies. One of the adjuvant studies showed an advantage for patients with ER-positive cancers who received the anti-estrogen Tamoxifen in addition to CMF. The investigators have developed further treatment protocols and the new project will be grant supported (CA30006).

The Workshop on "Clonogenic Assays and Chemotherapy Sensitivity" was held in February 1981. A staff activity was the issuance of RFP NCI-CB-14339: Biomedical Computing Software Services in Support of Breast Cancer Treatment Program. A number of excellent proposals were submitted and the transition to the new contractor has gone smoothly. The Data Center is heavily involved with the Biomarkers project, classifying all specimens, selecting panels for distribution and analyzing the test results.

Information Section

The responsibilities include: 1) The monthly production of the publication Intercom which provides up-to-date listings of scientific papers on breast cancer research in biology, epidemiology, diagnosis, and treatment by title, author and journal reference; a list of meetings and conferences related to the disease; and, abstracts of presentations made at Workshops. The publication is sent to investigators and institutions throughout the world, approximately 1700 copies are distributed monthly. 2) A monthly publication of Intracom which is similar to the listing of the scientific literature found in Intercom, however, it provides abstracts or summaries of the published literature as well as those on grant and contract activities. The publication is provided only to members of the staff of the Branch and to the Chairman of the BCTF Committee. 3) Responding to inquiries for literature searches by subject matter and by investigator. The resulting information is provided to staff, both of the Branch and to others in NCI, and to members of the Committee as well as to grantees or contractors.

The principal developments of Fiscal Year 1981 have been:

INTRACOM software has been enhanced to incorporate various improvements which include an author index and production on microfiche. Distribution of the microfiche publication to the Task Force Committee members has

begun. Opinion solicited by questionnaire has disclosed that some lack enthusiasm for the microfiche medium, although substantially all have access to a reader. About 1/3 of the group responded and this ratio, applied to the INTERCOM list, suggests that there are about 500 potential users world-wide. Under this assumption, global distribution can be managed with available resources at an annual cost of $7,500-10,000 for all charges, including postage and handling. The annual incremental cost for an additional user is $12-15.

PROGRAMMING has begun for the fast search service to be made available to the Committee members and ultimately to others. This service will transmit output by telecommunication and provide a turnaround time of 1-2 hours for many searches unless overload occurs. Thereby the breast cancer workers will be freed from the long delays which attend search queries submitted through library centers and will be able to exploit more effectively the growing power of automated information systems. The communication interfaces required have been installed on the 990 minicomputer.

SEARCH REQUESTS from the staff continue to increase, covering a wide range of subjects and sophistication. Capacity is ample, although turnaround time suffers occasionally when other work is pressing.

ADP UTILIZATION has not been fully effective in augmenting clerical productivity but further improvement should be possible with the major enchancement of WYLBUR introduced recently by DCRT.

Future Course

INTRACOM will receive a subject index as soon as the impending addition of medical subject headings to the CANCERLIT file is done by MEDLARS. The subject index will require a substantial programming effort but will complete the present plan for the development of INTRACOM.

The distribution of INTRACOM will be expanded.

SEARCH SERVICE by telecommunication will be instituted experimentally and evaluated for utility.

TELECONFERENCING, mentioned for the future in the previous report, was not reached but programming for it and some experimenting with it will be done if there is sufficient interest. This project will not be started until experience with the search service has provided some information concerning the terminal facilities of the users.

TRAINING of clerical personnel in the use of ADP procedures will continue.

The significance of the program is the facilitation of access to comprehensive and timely information concerning breast cancer that should enhance the quality of program formulation by staff and consultants.

BREAST CANCER TASK FORCE GRANT SUPPORTED STUDIES AND ONGOING CONTRACTS

DIAGNOSIS

I. Biophysical Tools for Detection and Diagnosis

RO1-CA-25836
Rational Design of Breast Tumor Localizing Agents
Katzenellenbogen, John University of Illinois

RO1-CA-28961
No-Dose Highly Magnified Mammograms to Aid Diagnosis
Galkin, Benjamin Thomas Jefferson University

RO1-CA-29993
Effects of X-Rays on Human Mammary Epithelial Cells
Smith, Helene University of California, Berkeley

RO1-CA-29940
Damage-Repair Studies Related to Mammography
Han, Antun/Elkind, Mortimer Argonne National Laboratory

RO1-CA-29781
Effects of Dose Rate on Rat Mammary Carcinogenesis
Shellabarger, Claire Brookhaven National Laboratory

II. Immunodiagnosis

RO1-CA-25653
Antigen-Antibody Complexes in Breast Cancer
Chu, Tsann Roswell Park Memorial Institute

RO1-CA-19083
T-Antigen in Human Cancer Detection
Springer, Georg Evanston Hospital

RO1-CA-29586
Immunocompetent Cells Infiltrating in Human Breast Cancer
Carmack, Holmes University of California, Los Angeles

RO1-CA-29601
Immunocompetent Cells Infiltrating Human Breast Cancer
Bhan, Atul Harvard Medical School

R23-CA-30370
Monoclonal Antibodies to Breast Cancer Immune Complexes
Papsidero, Lawrence Roswell Park Memorial Institute

*NO1-CB-84228
Cunningham-Rundles, Susanna Sloan-Kettering

NO1-CB-84224
Medof, Edward University of Chicago

III. Biologic Markers in Breast Cancer Preneoplasia

RO1-CA-25574
Isozymes Specific to Human Breast Neoplasia
Yang, Ning-Sun Michigan Cancer Foundation

RO1-CA-30636
Human Immune Responses to Murine Mammary Tumor Virus
Dion, Arnold Institute for Medical Research

NO1-CB-84222
Balinsky, Doris Iowa State University

NO1-CB-84316
Jensen, Hanne University of California, Berkeley

NO1-CB-84223
McCarty, Kenneth, Jr. Duke University

NO1-CB-74206
Schwartz, Morton Memorial Hospital

NO1-CB-53853
Schwartz, Morton Sloan-Kettering

NO1-CB-74086
Sussman, Howard Stanford University

IV. Morphologic Discriminants

R23-CA-31755
In Vitro Studies on Mammary Neoplastic Progression
Asch, Bonnie Roswell Park Memorial Institute

R23-CA-28128
Tissue Blood Group Antigens and Carcinogenesis
Howard, Donald Maine Medical Center

*For all contracts, see respective contract summary.

NO1-CB-74098
Page, David Vanderbilt University

NO1-CB-74097
Rosen, Paul Memorial Hospital

EPIDEMIOLOGY

I. Genetic Aspects of Susceptibility to Breast Cancer; Hormone Metabolism Patterns Associated with Familial High Risk

RO1-CA-27632
Genetic Epidemiology of Breast Cancer in Families
King, Mary-Claire University of California, Berkeley

RO1-CA-30069
Estradiol Glucuronidation and Breast Cancer
Zumoff, Barnett Montefiore Medical Center

II. Steroid Hormones (Endogenous and Exogenous) and Their Contribution to Breast Cancer Risk; Hormonal Aspects of First Pregnancy; Epidemiologic Risk Factors in Relation to Levels of Steroid Hormone Receptors and of Estrogen-Binding ß-Globulin

NO1-CB-53884
Nomura, Abraham University of Hawaii

NO1-CB-63996
Deubner, David Duke University

NO1-CB-74099
Slone, Dennis/Shapiro, Samuel Boston University

NO1-CB-74101
Preedy, John Emory University

PO1-CA-13556
Epidemiology and Natural History of Breast Cancer
Petrakis, Nicholas University of California, San Francisco

RO1-CA-28720
Breast Cancer Biology: Epidemiology and Prognosis
Deubner, David Duke University

RO1-CA-30069
Listed under I
Zumoff, Barnett Montefiore Medical Center

III. Thyroid Function in Relation to Breast Cancer Risk

NO1-CB-84230
Maloof, Farahe Massachusetts General Hospital

IV. Epidemiology of Histopathologic Subcategories of Breast Cancer

NO1-CB-53968
Stenkvist, Bjorn University Hospital of Uppsala

NO1-CB-63997
Rosen, Paul Memorial Sloan-Kettering

V. Epidemiology of Benign Breast Disease; Relation to Epidemiology and Natural History of Breast Cancer; Relation to Ethnicity and Risk of Breast Cancer

NO1-CB-74102
Modan, Baruch Chaim Sheba Medical Center

NO1-CB-74202
Spivey, Gary University of California, Los Angeles

NO1-CB-84231
Bartow, Sue University of New Mexico

RO1-CA-26021
Fibrocystic Breast Disease: Epidemiology and Histology
Kelsey, Jennifer Yale University

PO1-CA-13556
Listed under II
Petrakis, Nicholas University of California, San Francisco

RO1-CA-28223
Epidemiologic Study of Breast Cancer Risk Factors
Dupont, William Vanderbilt University

VI. Epidemiology of Minimal Breast Cancer

NO1-CB-74103
Pasternack, Bernard New York University Medical Center

VII. Environmental Risk Factors for Breast Cancer (beside exogenous hormones)

A. Diet (general; lipids and cholesterol; in relation to intestinal flora; in relation to hormone levels and metabolism; in relation to properties of the cell membrane; in relation to immune responsiveness and tumor cell susceptibility to cytotoxicity)

NO1-CB-53884
Nomura, Abraham University of Hawaii

NO1-CB-74104
Gorbach, Sherwood New England Medical Center

NO1-CB-84229
Kirschner, Marvin Newark Beth Israel Hospital

NO1-CB-84318
Papatestas, Angelos Mount Sinai School of Medicine

RO1-CA-30273
Dietary Fat Modulation of Mammary Tumorigenesis
Erickson, Kent University of Calfornia, Davis

RO1-CA-30629
Promotion of Breast Cancer: Lipid Hormone Interactions
Cave, William University of Rochester

B. Possible Carcinogens and Mutagens in Breast Fluids

PO1-CA-13556
Listed under II
Petrakis, Nicholas University of California, San Francisco

VIII. Correlation Between Breast Tumor Microscopic Characteristics and Patient Survival; Epidemiology, Morphology, Biochemistry, and Immunohistochemistry of Breast Tumors in Relation to Prognosis

RO1-CA-28720
Listed under II
Deubner, David Duke University

RO1-CA-30335
Immunohistochemical Profile and Survival in Breast Cancer
Lee, Arthur New England Medical Center

RO1-CA-30342
RNA Virus-Related Antigen in Breast Cancer and Prognosis
Mesa-Tejada, Ricardo Columbia University

IX. Antiviral Antibodies and Breast Cancer; Relation to Ethnicity, to Epidemiology and to Prognosis

RO1-CA-29711
Epidemiology and Etiology of Human Breast Cancer
Day, Noorbibi Memorial Sloan-Kettering

RO1-CA-30342
Listed under VIII
Mesa-Tejada Columbia University

EXPERIMENTAL BIOLOGY

I. Factors in the Induction of Mammary Tumors

RO1-CA-18664
Role of Prolactin in Mouse Mammary Tumorigenesis
Sinha, Yagya Scripps Clinic and Research Foundation

RO1-CA-27026
Basis for Mammary Gland Susceptibility to Carcinogenesis
Russo, Jose Michigan Cancer Foundation

RO1-CB-27293
Hormone Influences During Mammary Tumorigenesis
Socher, Susan Baylor College of Medicine

RO1-CA-20764
Neoplastic Mammary Gland: Structure/Function
Strum, Judy University of Maryland

RO1-CA-25915
The Radiobiology of Mouse Breast Preneoplasia
Cardiff, Robert University of California, Davis

RO1-CB-31207
Radioprotective Effect of Mammary Tumor Cell Grafts
Scarantino, Charles Bowman Gray School of Medicine

RO1-CA-21993
Normal and Neoplastic Development of the Mammary Gland
Dulbecco, Renato The Salk Institute for Biological Studies

RO1-CA-22879
Milk, Prolactin Binding and Thyroid in Breast Cancer
Goodman, David Albany Medical College of Union University

R23-CA-28999
MMTV in Spontaneous and Carcinogen-Induced Tumors
Pauley, Robert University of Miami

RO1-CA-30036
Mammary Metaplasia, Tumorigenesis and Chemoprevention
Sorof, Sam The Institute for Cancer Research, Fox Chase

RO1-CA-31774
Estrogen Action in Normal Mammary Gland
Haslam, Sandra Michigan State University

RO1-CA-30570
Modulation of Mammary Preneoplastic Progression
Medina, Daniel Baylor College of Medicine

RO1-CA-18946
Cell Surface Modulation in Mammary Neoplasia
Thompson, Karen Children's Hospital Medical Center

NO1-CB-84227
El-hawari, Monaem Midwest Research Institute, Kansas City

NO1-CB-84226
D'Ambrosio, Steven Ohio State University

II. Growth Passage and Characterization of Normal Mammary Epithelial Cells

PO1-CA-05388
Biology of Mammary Neoplasia
Nandi, Satyabrata University of California, Berkeley

RO1-CA-24844
Characterization of Human Mammary Cells
Stampfer, Martha University of California, Berkeley

RO1-CA-29090
Characterization of MNU-Induced Mammary Cancers
Grubbs, Clinton Southern Research Institute, Birmingham

NO1-CB-74094
Misfeldt, Dayton Stanford University

NO1-CB-74188
Masui, Hideo University of California, San Diego

III. Mammary Tumor Response to and Dependence on Hormones

RO1-CA-21606
Role of Estrogen and other Hormones in Breast Cancer
Butler, Barkley Michigan Cancer Foundation

RO1-CA-16660
Insulin and Estrogen Interactions in Breast Cancer
Hilf, Russell University of Rochester

IV. Interaction of Neoplastic Mammary Cells with other Cell Populations

RO1-CA-25179
The Fibrotic Response to Human Breast Carcinoma
Stern, Robert University of California, San Francisco

RO1-CA-20764
Listed under I
Strum, Judy University of Maryland

RO1-CA-28366
Natural Site Preference in Mammary Cancer Biology
Miller, Fred Michigan Cancer Foundation

RO1-CA-20122
Epithelial-Stromal Interactions of Breast Carcinoma
Armstrong, Rosa University of California, San Francisco

NO1-CB-84239
Spring-Mills, Elinor State University of New York

V. Cell Surface Proteins in Relation to Metastasis

RO1-CA-19814
Metabolic Fate of Mammary Cell Surface Glycoconjugates
Bernacki, Ralph Roswell Park Memorial Institute

RO1-CA-27909
Adhesive Interactions in Mammary Tumor Epithelial Cells
Buck, Clayton The Wistar Institute

RO1-CA-31695
Sialoglycoproteins of a Metastatic Mammary Tumor
Carraway, Kermit University of Miami

RO1-CA-19455
Use of Membranes to Assess Phenotypic Expression
Ceriani, Roberto Children's Hospital Medical Center

RO1-CA-08418
Glycoproteins from Cancer Cells
Codington, John Massachusetts General Hospital

RO1-CA-27314
Plasma Membrane and Metastasis in Rat Mammary Cancer
Fairbanks, Grant Worcester Foundation

RO1-CA-20605
Mammary Cancer and Hormone Induced Responses
Clark, James Baylor College of Medicine

RO1-CA-30171
Steroid Hormones in Breast Cancer
Hockberg, Richard Yale University

RO1-CA-26869
Nuclear Estrogen Receptors in Breast Cancer
Horwitz, Kathryn University of Colorado Medical Center

RO1-CA-18664
Listed under I
Sinha, Yagya Scripps Clinic and Research Foundation

RO1-CA-27293
Listed under I
Socher, Susan Baylor College of Medicine

RO1-CA-28645
Vitamin B6 and Hormone Action in Uteri and Breast Cancer
Wotiz, Herbert Boston University School of Medicine

RO1-CA-28698
Perinatal Estradiol Influence on Mammary Development
Warner, Marlene Baylor College of Medicine

RO1-CA-28393
Neonatal Hormone Exposure and Mammary Tumorigenesis
Talamantes, Frank University of California, Santa Cruz

RO1-CA-18458
Fetal Exposure to Hormones and Mammary Carcinogenesis
Boylan, Elizabeth Queens College of CUNY

RO1-CA-16464
Iodinated Estrogens in Breast Cancer
Caspi, Eluahu Worcester Foundation for Experimental Biology

RO1-CA-22343
Mechanism of Antiestrogen Action in Breast Cancer
Chamness, Gary University of Texas Health Science Center

RO1-CA-24687
Metabolism of Estrogens and Androgens by Breast Cancer Cells
Macindoe, John University of Iowa

R23-CA-29501
Estrogen Responsiveness in Human Breast Cancer
Moore, Michael Marshall University

RO1-CA-26825
Antigen Specific NK Activity and Suppression in MMTV
Lane, Mary-Ann Sidney Farber Cancer Institute

RO1-CA-25418
Murine Virus Cross-Reacting Antigen in Human Tissue
Hackett, Adeline University of California, Berkeley

RO1-CA-28844
Mammary Carcinoma Metastasis
Nicolson, Garth University of Texas System Cancer Center

VI. Prevention of Neoplastic Transformation

RO1-CA-30036
Listed under I
Sorof, Sam The Institute for Cancer Research, Fox Chase

NO1-CB-74207
Moon, Richard IIT Research Institute

VII. Pathophysiology of the Solid Mammary Carcinoma and its Relation to Metastasis

PO1-CA-05388
Listed under II
Nandi, Satyabrata University of California, Berkeley

RO1-CA-29537
Osteotropism of Mammary Carcinoma Metastasis
Mundy, Gregory University of Texas Health Science Center

RO1-CA-28735
Proteoglycans and Basal Structure and Function
Bernfield, Merton Stanford University

VIII. Immunodiagnosis and Immunoprevention of Cancer Growth and Progression

RO1-CA-27437
Immune Reactivity and Mammary Neoplasia
Heppner, Gloria Michigan Cancer Foundation

RO1-CA-30284
An Immunodiagnostic Assay for Breast Cancer Detection
Gaffney, Edwin The Pennsylvania State University

RO1-CA-20286
Breast Neoplasia Diagnosis with Specific Antibodies
Ceriani, Roberto Children's Hospital Medical Center

XI. Service, Support and Resources

R13-CA-30294
Gordon Conference on Mammary Gland Biology
Hilf, Russell University of Rochester Medical Center

R13-CA-28816
Mammary Cancer in Animals and Man - Conference
Hageman, Philomena Netherlands Cancer Institute

NO1-CB-74175
Bogden, Arthur Mason Research Institute

NO1-CB-84225
Furthmayr, Heinz Yale University School of Medicine

NO1-CB-84314
Goldberg, Burton New York University Medical Center

TREATMENT

I. Steroid Receptors and Mammary Carcinoma

A. Physiologic Behavior

RO1-CA-27470
Receptor Studies in Human Breast Cancer
Hollander, Vincent Hospital for Joint Diseases

RO1-CA-26452
Studies of Anomalous Receptors in Breast Cancer
Panko, Walter Baylor College of Medicine

RO1-CA-22828
Fate of Steroid Hormones in Breast Tumor Cells
Brooks, Sam Wayne State University School of Medicine

B. Methodology

RO1-CA-29971
Histochemical Methods for Receptors in Breast Cancer
Chamness, Gary University of Texas Health Science Center

NO1-CB-23862
McGuire, William University of Texas Health Science Center

NO1-CB-43969
Jensen, Elwood University of Chicago

C. Evaluation of Clinical Application

NO1-CB-04338
Thomas, David Fred Hutchinson Cancer Research Center

II. Biologic Markers in Breast Cancer

A. Serum Resource, Storage and Distribution

NO1-CB-74138
Rodes, Ned Cancer Research Center, Columbia, MO

NO1-CB-74213
Bowman, Harold Butterworth Hospital

NO1-CB-74137
Whitney, Leslie Wilmington Medical Center

NO1-CB-84296
Go, Vay Liang Mayo Foundation

G. Research Studies

RO1-CA-26935
CEA and FHAP as Breast Cancer Management Parameters
Tormey, Douglass University of Wisconsin

NO1-CB-43900
Dao, Thomas Health Research, Inc.

NO1-CB-74204
Hilf, Russell University of Rochester

III. Mechanisms of Treatment Action

NO1-CB-84221
Das Gupta, Tapas University of Illinois

RO1-CA-26004
Therapy Effects on Tumor Kinetics and Immune Parameters
Fisher, Bernard University of Pittsburgh

RO1-CA-25586
Therapy-Induced Alterations in Breast Cancer
Panko, Walter Baylor College of Medicine

RO1-CA-24129
Control of Breast Cancer by Serum Growth Factors
Osborne, Kent University of Texas Health Science Center

RO1-CA-02071
Estrogen Metabolism and Action in Pregnancy and Cancer
Levitz, Mortimer New York University

RO1-CA-30251
Hormone Priming and Chemotherapy in Primary Breast Cancer
Osborne, Kent University of Texas Health Science Center

RO1-CA-23079
Steroid Sulfurylation Inhibitors as Antitumor Agents
Horwitz, Jerome Michigan Cancer Foundation

RO1-CA-05197
Endocrine Factors Influencing Tumor Growth in Man
Pearson, Olof Case Western Reserve University

IV. Preclinical Treatment Testing: Animal Models

RO1-CA-29006
C. Parvum Therapy of Mammary Carcinoma Metastases
Kreider, John Pennsylvania State University

RO1-CA-26287
Canine Model for Human Breast Cancer Immunotherapy
Hurvitz, Arthur The Animal Medical Center

V. Clinical Investigations

NO1-CB-43917
Giuliano, Armando University of California, Los Angeles

NO1-CB-43990
Hubay, Charles Case Western Reserve University

NO1-CB-33899
Ahmann, David Mayo Foundation

NO1-CB-53917
Scanlon, Edward Evanston Hospital

NO1-CB-53851
Santen, Richard Pennsylvania State University

RO1-CA-30006
Chemotherapy and Anti-Estrogen Therapy in Breast Cancer
Hubay, Charles Case Western Reserve University

VI. Data Management Resource

NO1-CB-74140
Dunsmore, Marlene Mason Research Institute

NO1-CB-14339
Dunsmore, Marlene Information Management Services, Inc.

CONTRACT RESEARCH SUMMARY

Title: Estrogen Replacement after Premenopausal Oophorectomy and Breast Cancer Risk

Principal Investigator: Dr. Dennis Slone, Dr. Samuel Shapiro
Performing Organization: Boston University Medical Center
City and State: Cambridge, MA

Contract Number: NO1-CB-74099
Starting Date: 9/1/77 Expiration Date: 8/31/82

Goal: To examine the hypothesis that exposure to female hormones, particularly estrogen replacement therapy, is related to an increased risk of breast cancer, either during use or after a latent interval.

Approach: An epidemiological study of the case-control type is being implemented as part of an ongoing, hospital-based, multicenter data collection system. Cases of breast cancer and potential controls, women with a variety of non-malignant conditions, are interviewed by trained nurse monitors in hospitals throughout the country. Information on lifetime drug use and relevant medical data are recorded on standard forms and transferred to computer files for analysis.

Progress: As of the end of September 1980, 1,685 women with breast cancer had been studied. Of these, 1,222 (73%) were newly diagnosed, of whom 110 (9%) were menopausal because of bilateral oophorectomy. Preliminary data do not provide any overall evidence that non-contraceptive estrogen use by women with premenopausal bilateral oophorectomy increases the risk of breast cancer. In the final analysis, the data will be stratified on risk factors for breast cancer, such as benign breast disease, parity and age at first pregnancy. As yet, numbers are insufficient to do this. Women with breast cancer are currently being interviewed at a rate of 600 per year.

Project Officers: Elizabeth P. Anderson, Ph.D., Robert Hoover, M.D.
Program: Breast Cancer Epidemiology
FY 81 Funds: $36,000

CONTRACT RESEARCH SUMMARY

Title: Biological Markers in Breast Cancer: Patient Resource

Principal Investigator: Dr. Harold E. Bowman
Performing Organization: Butterworth Hospital
City and State: Grand Rapids, MI

Contract Number: NO1-CB-74213
Starting Date: 9/15/77 Expiration Date: 9/14/82

Goal: To develop a Breast Cancer Task Force specimen resource for blood from breast cancer patients, benign disease patients, and controls to be used in a search for and verification of new breast cancer markers.

Approach: Thirty milliliters of blood will be collected from breast disease patients who are scheduled to undergo biopsy and/or primary surgery for breast lesions prior to surgery. Another specimen will be collected, when feasible, 5-10 days postmastectomy from the same patient. Annual drawings are made on patients with malignant diagnosis. Patients with benign tumors are requested to complete annual questionnaires for a period of two years after biopsy. Serum specimens will be stored at -70°C, then shipped to an NCI-designated blood bank facility with appropriate clinical data.

Progress: After a formal presentation to the surgery sections in each participating hospital, surgeons who perform 95% of all breast biopsies in these hospitals signed letters of agreement allowing their patients to enter directly into the study. Since the inception of the program, 2,029 patients have been entered into the study; 435 of these patients have been found to have malignant breast disease. Approximately 26,000 vials containing serum specimens have been shipped to the central storage facilities at Mayo Clinic. 238 collections have been made on the annual anniversary of malignant patients and almost 1,000 benign follow-up questionnaires have been completed on benign patients. This information has been forwarded to Mason Research computer bank. Fifteen months into the program, all participating patients and interested parties were invited to an informational update presentation provided by NCI project officers. The audience, numbering close to 500, were congratulated for their participation and encouraged to continue their cooperative efforts. Participating surgeons, pathologists, and hospital personnel working in the program attended a similar informational session.

Project Officers: Ihor J. Masnyk, Ph.D., Mary E. Sears, M.D.
Program: Breast Cancer Treatment
FY 81 Funds: $46,550

CONTRACT RESEARCH SUMMARY

Title: Biologic Markers in Breast Cancer: Patient Resource

Principal Investigator:	Dr. Ned D. Rodes
Performing Organization:	Cancer Research Center
City and State:	Columbia, MO
Contract Number:	NO1-CB-74138
Starting Date:	9/1/77
Expiration Date:	8/31/82

Goal: To serve as a Breast Cancer Task Force specimen resource for blood from breast cancer patients and controls to be used in a search for and verification of new breast cancer markers.

Approach: Thirty milliliters of blood are collected from volunteer Breast Cancer Detection Project and Women's Cancer Control Program screenees after they have signed appropriate consent forms. In the event of subsequent breast biopsies upon any of the participants, a 30 ml postoperative specimen will also be collected from postmastectomy cases within three months. In addition, prebiopsy and postmastectomy blood samples will be obtained from hospitalized ladies in the Columbia area who agree to participate in the program. Emphasis will be placed upon the collection of samples from hospitalized patients as opposed to specimen collection from normal volunteer screenees. No special requirements will be placed upon the participants in terms of diet or liquid intake. Anniversary serum from malignant patients will be obtained for three, possibly five years. All blood will be stored at -70°C, and then shipped to NCI-designated blood bank facility with appropriate clinical data.

Progress: In 40 months of serum collection (from 12/77 to 4/81), 11,379 individual samples of blood were fully processed; this number of blood samples yielded 122,080 vials. The average serum collection per participant has been 10.0 ml. The average amount of serum per vial was 1.1 ml. The total number of "voids" (no draws; broken clot tubes; collapsed veins; hemolysis; etc.) was limited to 426 over the entire collection period. The average acceptability for research of shipments during this time frame was 96.2%. Surgeons at the Ellis Fischel State Cancer Hospital have agreed to allow our blood collection team access to their hospitalized, pre-breast biopsy patients. Three more hospitals in the area are currently bringing this matter under administrative review. If they agree to cooperate, all the non-federal hospitals in the Columbia area will be indirect participants in this NCI study.

Project Officers: Ihor J. Masnyk, Ph.D., Mary E. Sears, M.D.
Program: Breast Cancer Treatment
FY 81 Funds: $52,250

CONTRACT RESEARCH SUMMARY

Title: Therapy for Stage II or Stage III Carcinoma of the Breast

Principal Investigator: Dr. Charles A. Hubay
Performing Organization: Case Western Reserve University
City and State: Cleveland, OH

Contract Number: NO1-CB-43990
Starting Date: 6/16/74 Expiration Date: 6/15/82

Goal: This clinical trial was initiated in September 1974, to determine if combined chemotherapy (CMF), anti-estrogen therapy (Tamoxifen) and immunotherapy (BCG) following mastectomy in Stage II, III breast cancer would yield better results than when used later in the course of the disease when recurrence became manifest.

Approach: Patients under age 76 who show axillary nodes involved with metastases at the time of surgery were eligible for this study. Stratification, but not treatment selection, was on the basis of the presence or absence of estrogen receptor protein (ER) in the tumor. Random treatment assignments were (1) cyclophosphamide, methotrexate, 5-fluorouracil (CMF); (2) cyclophosphamide, methotrexate, 5-fluorouracil, Tamoxifen (CMFT); and (3) CMFT for 12 months plus BCG for 12 months. Endpoint was the first evidence of treatment failure, i.e., the appearance of local recurrence or of distant tumor.

Progress: This study was closed in June 1979. Three hundred eighteen patients were enrolled in the study. Of these, 76% had estrogen receptor (ER) positive tumors ($\geq$ 3 femtomoles/mg of protein). All patients have completed one year of chemotherapy. Twenty patients are completing their 12 months of BCG therapy. Of the treated patients, 48 have died and 96 have had treatment failure. Thirty-three patients have withdrawn voluntarily after one month to one year of therapy. Chemotherapy was not accompanied by significant myelosuppression. Hair loss was slight. Tamoxifen, the antiestrogen agent used, was tolerated well, without serious side effects, although most patients experienced hot flashes while on the drug. Ninety-six patients have had recurrence; 35 in the CMF group, 30 in the CMF + Tamoxifen, and 31 in the CMF + Tamoxifen + BCG group. Statistical comparison for treatment failure between Stage II ER positive and ER negative patients is significant at the $p < 0.0001$ level, with the latter group recurring more rapidly (48.6% vs. 38.8% at 48 months). Relapse rate for the Stage II treated patients at 48 months is as follows: CMF 44.5%, CMF + Tamoxifen 40.0% and CMF + Tamoxifen + BCG 40.4%. Recurrence rates between Stage II patients with 1-3 positive nodes are significantly different when stratified according to estrogen receptor values, with higher relapse rates in the ER negative group.

Stratification by estrogen receptor assay shows a significant difference in recurrence when Tamoxifen is added to CMF therapy in ER+ patients ($p = 0.03$). There is no difference in recurrence rates for ER negative patients with any of the three treatments used. Survival data at 48 months mean follow-up show a significant mortality for the ER negative patients vs. ER+ patients ($p < 0.0001$).

Project Officer: Mary E. Sears, M.D.
Program: Breast Cancer Treatment
FY 81 Funds: $75,000

CONTRACT RESEARCH SUMMARY

Title: Epidemiology of Benign Breast Disease

Principal Investigator: Dr. Baruch Modan
Performing Organization: Chaim Sheba Medical Center
City and Country: Tel Hashomer, Israel

Contract Number: NO1-CB-74102
Starting Date: 8/1/77 Expiration Date: 7/31/81

Goal: To determine the characteristics of patients with different types of noninvasive breast lesions, with particular reference to diet and to those factors reputed to be preferentially associated with breast cancer, and to compare the findings with our similarly conducted breast cancer study.

Approach: The study consists of two phases: (a) case-control interview study of 600 cases of noninvasive breast diseases in terms of such risk factors as: dietary habits, age at first birth, menstrual history, menopausal status, parity, height and weight, familial breast cancer, selected drug history, and previous radiation exposure; and (b) an incidence study of noninvasive breast lesions in a total community. The characterization of the breast lesions will take account of the histological pattern, degree of atypia, and lymphoreticuloendothelial response (LRE). Particular attention will be paid to the relative frequency of distinct histopathological forms in highand low-risk subpopulations (i.e., Europeans, Asian-African born).

Progress: As of November 1980, 2,180 interviews have been conducted: 874 cases, 709 surgical controls and 597 neighborhood controls. All the interviews have been performed at home. All of the histopathological slides have been read by both study pathologists. The frequency distributions of cases by conventional pathological criteria are as follows: fibroadenoma 179, proliferative 361, microcystic 117, intraductal papilloma 14, combined histology 53, in situ carcinoma 18, nonspecific histopathology 82, cystosarcoma 7, granuloma 46; according to Black's gradings: Grade 1: 361, Grade 1-2: 3, Grade 2: 204, Grade 2-3: 131, Grade > 3: 95. Previous surgery has been validated. The incidence study of the whole spectrum of breast disease began in July 1979, and collection of slides and cases has been concluded. The study includes demographic and pathological data; 80% of the histological slides have been reviewed using the Black classification. Approximately 4,200 cases have been included up to now.

Project Officer: Elizabeth P. Anderson, Ph.D.
Program: Breast Cancer Epidemiology
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Epidemiologic Characteristics of Pre- and Postmenopausal Breast Cancer

Principal Investigator: Dr. David C. Deubner
Performing Organization: Duke University Medical Center
City and State: Durham, NC

Contract Number: NO1-CB-63996
Starting Date: 6/30/76 Expiration Date: 1/31/81

Goal: To define the epidemiologic characteristics of breast cancer in pre- and postmenopausal women, and of breast cancers rich and poor in cytoplasmic receptors for estrogen and progesterone.

Approach: This case-referent study is of breast cancer patients undergoing surgery at university and community hospitals, surgical and medical patients not having breast or gynecological surgery at the same hospitals, and subjects from the community. Data collection is by interview of all subjects and review of charts of hospital patients. Laboratory studies on tissue and serum from breast cancer patients include quantitative estrogen and progesterone receptor determinations, evaluation of histology and ultrastructure by a standardized protocol, and estrogen and progesterone serum determinations. Statistical analyses estimate the relative strength of association between breast cancer in pre- and postmenopausal women and such factors as age of menarche, age of first delivery, obesity, and family history of breast cancer. Associations are also being sought between these factors and concentrations of the cytoplasmic hormone receptors.

Progress: As of November 1980, collection and computer entry of interview, hospital chart review, and estrogen receptor data was complete. Light microscopy review was complete and ultrastructure review well under way. Analyses of interview data relevant to the epidemiology of pre- and postmenopausal breast cancer, and to the epidemiology of estrogen receptors, are also complete and are being prepared for publication.

Project Officers: Elizabeth P. Anderson, Ph.D., Gordon B. Cutler, M.D.
Program: Breast Cancer Epidemiology
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Biologic Characterizations of "Premalignant" Human Mammary Epithelial Hyperplasias

Principal Investigator: Dr. Kenneth Scott McCarty, Jr.
Performing Organization: Duke University
City and State: Durham, NC

Contract Number: NO1-CB-84223
Starting Date: 8/1/78 Expiration Date: 7/31/81

Goal: To characterize potentially "premalignant" epithelial lesions of the human breast using biochemical, morphologic and immunologic techniques.

Approach: Analyses are performed on lesions observed in subcutaneous mastectomy specimens and benign biopsies. These are compared to carcinomatous areas of breast cancer specimens. Lesions are classified by subgross, light, and electron microscopic techniques as appropriate. The tissues are evaluated for the presence of measurable steroid receptors, estrogen-progesterone binding proteins, endogenous peroxidase, K-casein, and CEA. Immunologic characterizations include immunohistologic assessment of IgG, IgA, IgM and the expression of ABH blood group antigens and/or the unmasking of component antigens.

Progress: The effects of the menstrual cycle on the normal and fibrocystic mammary gland have been characterized and categorized into five phases: 1) proliferative (days 3-7), 2) follicular phase of differentiation (days 8-14), 3) luteal phase of differentiation (days 15-20), 4) secretory (days 21-27), and 5) menstrual (days 28-2). A statistically significant association of the simultaneous presence of certain patterns of intraacinar epithelial hyperplasias and carcinoma has been confirmed. Apocrine and adenosquamous differentiation have been characterized ultrastructurally. Attenuation of the epithelial stromal junction was associated with IgG localization and alteration in the ABH blood group antigen expression in mammary dysplasias. CEA is seen in malignant lesions and severe epithelial dysplasias but only rarely (< 5%) in the simple fibrocystic lesions. K-Casein does not appear to correlate with E_2 receptor. The localization of immunoglobulin G in a pericellular pattern has been observed in dysplastic epithelial hyperplastic lesions (usually type 14 positive), while apical IgA localization has characterized the non-dysplastic benign lesions studied. IgG localization correlates with lymphopenia. FITC labeled steroids to localize sex steroid binding have suggested that 17 substituted compounds correlate best with SDGA techniques, although E_2-FITC binding to low-affinity high-capacity proteins is likely due to the correlation of binding to the presence of estrogen-progesterone binding protein. Menstrual cycle fluctuations of estrogen and progesterone receptor have been observed in benign, dysplastic and malignant lesions. The levels of intermediate affinity estrogen-progesterone binding protein are maximal in the late luteal phase.

Project Officer: D. Jane Taylor, Ph.D.
Program: Breast Cancer Diagnosis
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Endocrine Events at the Time of First Pregnancy

Principal Investigator: Dr. John R. K. Preedy
Performing Organization: Emory University School of Medicine
City and State: Atlanta, GA

Contract Number: NO1-CB-74101
Starting Date: 8/1/77 Expiration Date: 7/31/82

Goal: It is proposed that the protective effect of an early first pregnancy against breast cancer is due to a change in the hormonal environment following that event. We proposed to investigate and characterize such a change.

Approach: Nulliparous subjects in the 18-22 age range who have not taken birth control pills, who have a history of normal regular menses, and who are planning pregnancy in the next 1-2 years will be selected (Group A). Similar subjects will be chosen who do not plan to become pregnant in the next 1-2 years (Group B). Similar subjects to the above but in the age range 30-40 would also be selected (Groups C and D). All groups would have the following carried out in the early follicular phase of the menstrual cycle: plasma gonadotropins, estrogens, progesterone, androgens; urine estrogens and androgens; plasma protein-steroid binding studies; perphenazine-prolactin stimulation test; LRH-LH stimulation test. Results from Groups A, B, C, and D would be compared by appropriate analysis of variance techniques to determine significant contrasts among the four groups.

Progress: The total number of subjects participating in the program is 122. Group A - 41 (Initial study has been done on all 41. Twenty have become pregnant and four of these have suffered miscarriage. Fourteen have reached full term and delivered and the remaining two are still pregnant. Four of the subjects who have delivered have been restudied). Group B - 29 (All 29 have undergone the initial study and ten have been restudied). Group C - 24 (All 24 have undergone the initial study. Ten have become pregnant and one of these has suffered a miscarriage. Nine have so far delivered and one of these has been restudied). Group D - 28 (All 28 have undergone the initial study and nine of these have been restudied).

Project Officer: Elizabeth P. Anderson, Ph.D.
Program: Breast Cancer Epidemiology
FY 81 Funds: $27,000

CONTRACT RESEARCH SUMMARY

Title: Therapy of Patients with Stage II or Stage III Carcinoma of the Breast

Principal Investigator: Dr. Edward F. Scanlon
Performing Organization: Evanston Hospital
City and State: Evanston, IL

Contract Number: NO1-CB-53917
Starting Date: 6/30/75 Expiration Date: 6/29/82

Goal: To determine the efficacy of adjuvant chemotherapy and chemoimmunotherapy for patients who have had standard surgical intervention for Stage II or III carcinoma of the breast.

Approach: Patient accrual began in July 1975, and was completed as of July 1979. A total of 194 patients were entered into the study during this time. Stratification and randomization were carried out along with a balancing for prognostic factors according to the following variables: primary tumor size, number of positive nodes, menopausal status, and unfavorable local signs. The statistical analysis involved sequential treatment assignment and was designed to provide the greatest balance among the three groups. Using this method, patients were originally assigned to one of three treatment schedules: Group I - Oral phenylalanine mustard (L-Pam), Group II - 5-Fluorouracil, cyclophosphamide and prednisone (CFP), and Group III - CFP plus BCG inoculations. Enrollment in the single arm treatment, Group I, was discontinued in November 1977 because of a disproportionately high recurrence rate in the group at that time. The 38 patients already enrolled in that group at that time. The 38 patients already enrolled in that group remained to finish their single arm treatment. New patients from that time were enrolled either in Group II or III.

Progress: Fifty-six patients have experienced recurrent disease. Fifteen of the 38 patients in the L-Pam group (39%) report recurrences. Of the 78 patients in the CFP group, 22 (28%) report recurrences. Of the 78 patients in the third group, CFP + BCG, 19 (24%) report recurrent disease. At the time enrollment was discontinued in the L-Pam group, a higher recurrence rate was observed in that group than in the polychemotherapy groups. Since that time, the recurrence rate has dropped for the single arm treatment group, and the recurrence rate for the polychemotherapy groups has steadily increased. Currently, no statistically significant difference exists among the three treatment groups with regard to disease-free interval. Two prognostic factors, tumor size ($\geq$ 3 cm) and nodal involvement ($\geq$ 4), have emerged as statistically significant in terms of prognosis. We will be continuing to follow these patients very closely over the next few years in order to determine disease-free interval and, ultimately, survival. Data are also currently being combined with data from the Mayo Clinic study, which is similar in design to this project, in order to provide a larger patient population for analysis.

Project Officer: Mary E. Sears, M.D.
Program: Breast Cancer Treatment
FY 81 Funds: $36,000

CONTRACT RESEARCH SUMMARY

Title: Evaluation of the Impact of the Estrogen Receptor Assay on the Treatment of Human Breast Cancer

Principal Investigator:	Dr. David B. Thomas
Performing Organization:	Fred Hutchinson Cancer Research Center
City and State:	Seattle, WA

Contract Number: NO1-CB-04338
Starting Date: 9/1/80 Expiration Date: 6/30/82

Goal: To identify characteristics of women, their physicians and hospitals that distinguish individuals with breast cancer who have steroid hormone receptor assays performed on samples of their primary or recurrent tumor tissue; and to determine whether therapy for primary or recurrent disease is altered by the assay results.

Approach: Women with primary breast cancer in 1977-78 and 1980, and women in the former group who develop recurrent disease by the end of 1981 are identified through the Cancer Surveillance System (CSS) which is a population-based tumor registry that has been used to collect data on all newly diagnosed cancer cases in a 13-county area of Washington State since 1974. Descriptive information on all study subjects is being collected from the registry and this is supplemented by data on some women with disease onset in 1977-78 that were collected by personal interviews as part of a previous study. Information on steroid receptor assays is collected from medical records. Information on physicians is obtained from professional directories and a state survey of physicians; and data on hospitals are abstracted from similar sources. Histologic and clinical characteristics of the tumor and types of therapies given are obtained from CSS records and will be supplemented by querying physicians. Assay methods used and quality control procedures followed will be ascertained from laboratory directors.

Progress: A total of 1,206 female residents of King County who developed breast cancer in 1977 or 1978 were identified. Information on steroid assays, recurrences of disease, and therapy for recurrent tumors is currently being collected. Women who are residents of the 13-county catchment area and who develop breast cancer in 1980 are being identified as they are detected by registry personnel and information on steroid receptor assays is being collected at the same time that routine data for the registry are being collected as physicians are identified through the registry. Data on all area hospitals have been obtained.

Project Officer: Mary E. Sears, M.D.
Program: Breast Cancer Treatment
FY 81 Funds: 0 ($105,073 funded by NIH-OD)

CONTRACT RESEARCH SUMMARY

Title: Steroid Sulfation and Estrogen Binding in Human Breast Cancer

Principal Investigator: Dr. Thomas L. Dao
Performing Organization: Health Research, Inc.
City and State: Buffalo, NY

Contract Number: NO1-CB-43900
Starting Date: 2/1/74 Expiration Date: 1/31/82

Goal: To determine the relationship of steroid sulfotransferase activity to estrogen receptor protein levels, to pathologic staging, and to risk of relapse.

Approach: Steroid sulfating enzyme activity and estrogen receptor (ER) levels have been assayed in breast tissue obtained from approximately 300 patients in three institutions. The evidence will be evaluated for or against correlation of the steroid sulfotransferase activity with risk for tumor metastasizing potential and with histopathologial parameters. The predictive potentials of ER and sulfation activity will be compared.

Progress: A total of 266 patients from three cooperating institutions were entered into the study between March 1974 and June 1976, inclusive. The average length of follow-up is now approximately 56 months. The data have been analyzed according to the following categories: DHEAS versus other prognostic indicators; E_2S versus other prognostic indicators; ER versus other prognostic indicators; and the recurrence rate for categories of prognostic indicators. The prognostic indicators considered were: age at diagnosis, pathological size of the tumor, histologically positive axillary nodes, and menopausal status. The synthesis of sulfotransferase was also evaluated for its correlation with age at diagnosis, tumor size, axillary nodal metastasis, and menopausal status. However, because of size, ER and sulfotransferase activities could not be measured in all tumors. The present analysis includes only those patients for whom both measurements were done. The data revealed that (1) DHEAS and E_2S are highly correlated with each other. Although there is a trend for DHEAS to increase with the size of the tumor, this association is not statistically significant. (2) ER levels are significantly correlated with the patient's age at diagnosis, the size of the tumor, and menopausal status. The ratio of DHEAS + $1/E_2S$ + 1 is significantly correlated with ER levels; ER levels and this ratio are negatively correlated. (3) The ratio of DHEAS + $1/E_2S$ + 1 is significantly correlated with the recurrence rate, and appears to be an independent variable. The recurrence rate is significantly lower in patients whose tumors have a ratio of < 1.5, whereas in contrast, the recurrence rate is higher in patients having a ratio of >1.5. This is true in patients having no nodal metastasis, as well as in those having 4+ nodes involved.

Project Officer: Mary E. Sears, M.D.
Program: Breast Cancer Treatment
FY 81 Funds: $10,000

CONTRACT RESEARCH SUMMARY

Title: Prevention of the Formation and Progression of Mammary Gland Preneoplastic Lesions

Principal Investigator: Dr. Richard D. Moon
Performing Organization: IIT Research Institute
City and State: Chicago, IL

Contract Number: NO1-CB-74207
Starting Date: 8/29/77 Expiration Date: 2/28/81

Goal: To study the use of retinoids to prevent the development and/or progression of preneoplastic lesions of the mammary gland.

Approach: Experimental animals are fed nontoxic levels of synthetic vitamin A analogues (retinoids) as a dietary supplement in the attempt to inhibit the development and progression of preneoplastic lesions in the mammary glands of mice and carcinogen-treated rats. Endpoints monitored are: incidence of hyperplastic alveolar nodules (HAN) and "spontaneous" mammary tumors in C3H/He mice, and incidence, latency, and multiplicity of chemical carcinogen-induced mammary tumors in Sprague-Dawley rats. The effects of beginning retinoid administration at various times after carcinogen administration are being examined, as is the influence of retinoid administration combined with bilateral ovariectomy of carcinogen-treated animals.

Progress: Previous studies have shown that combination treatment of the retinoid and a prolactin suppressor was more effective in inhibiting MNU-induced mammary carcinogenesis than either treatment alone. Thus, studies were initiated to determine the effect of retinoids on prolactin-induced mammary gland differentiation in organ culture. Both all-trans-retinoic acid and 4-hydroxyphenyl retinamide (4-HPR) inhibited lobular development and reduced the number of ductal branchings. Also, 4-HPR exerted a dose-related inhibitory effect on mammary parenchymal cell DNA synthesis. Furthermore, other data indicated that the inhibitory effect of 4-HPR on prolactin-induced mammary gland differentiation may be mediated by retinoic acid binding proteins. In other studies in which a 100% MNU-induced mammary tumor incidence with more than 4 tumors per rat was attained, tumor incidence in ovariectomized, 4-HPR-treated animals was 0. Thus it appears that 4-HPR is highly effective in inhibiting the induction of ovarian hormone independent mammary cancers. Moreover, the combination treatment of ovariectomy and retinoid was also highly effective in inhibiting the appearance of a second tumor when retinoid treatment was initiated following the surgical removal of the first tumor. Additional studies in pregnant and lactating rats indicate that the levels of retinoid receptor in the mammary tissue may be directly related to the circulating levels of estradiol in the animal.

Project Officer: Chester V. Piczak, B.S., D. Jane Taylor, Ph.D.
Program: Breast Cancer Experimental Biology
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Biomedical Computing Software Support of Breast Cancer Treatment Program

Principal Investigator: Ms. Marlene Dunsmore
Performing Organization: Information Management Services, Inc.
City and State: Bethesda, MD

Contract Number: NO1-CB-14339
Starting Date: 3/31/81 Expiration Date: 3/30/82

Goal: To increase the usefulness of the data generated in projects sponsored by the Breast Cancer Task Force Treatment Program and in other designated projects related to the treatment of human breast cancer.

Approach: A central file was developed by the initial contractor for three areas of study: (1) surgical adjuvant therapy, (2) tumor biomarkers, and (3) estrogen receptor assays. The file allows comparisons of the results from various studies and provides a data base from which material can be quickly and conveniently retrieved. This data file is also intended for testing new ideas, identifying groups of subjects suitable for more detailed study, and for preparing reports to the medical community and the general public. The file is not intended to duplicate those at individual institutions, but to prepare data for analyses that are not possible at the individual institutions. The current contractor will continue this data file.

Progress: The transition of the Breast Cancer files and belongings to I.M.S. went smoothly. Communication with the collaborating institutions has been maintained.

Project Officers: Mary E. Sears, M.D., Ihor Masnyk, Ph.D.
Program: Breast Cancer Treatment
FY 81 Funds: $149,445

CONTRACT RESEARCH SUMMARY

Title: Isoproteins in Normal, Benign and Malignant Breast Tissues

Principal Investigator: Dr. Doris Balinsky
Performing Organization: Iowa State University
City and State: Ames, IA

Contract Number: NO1-CB-84222
Starting Date: 8/1/78 Expiration Date: 7/31/81

Goal: To detect, quantitate, and characterize various isozymes or isoproteins in normal, benign and neoplastic breast tissue in an attempt to identify "tumor markers" which may have significance in the early detection of breast cancer or identification of patients with occult dissemination after local treatment.

Approach: A number of enzymes known to have differing isozyme patterns in different tissues will be assayed in human normal, benign, malignant and metastatic breast tissues. Isozyme patterns of those enzymes having detectable activity will be examined by electrophoresis. Subsequently, those isozymes showing differences between normal and malignant tissues will also be examined in sera from these patients. If interesting isozyme differences are found between normal and cancerous tissues, the isozymes will be purified and characterized. These studies could indicate altered metabolic status of the tumor. The data will be correlated with data on estrogen and progesterone receptors on the same material and with clinical and histopathologic data.

Progress: Twenty-three different sets of isozymes have been examined to date using cellulose acetate electrophoresis. The isozyme patterns of lactate dehydrogenase (LDH), malate dehydrogenase (MDH) and the esterases appear the most promising as tumor markers. LDH_5 generally predominated in breast carcinoma, while LDH_3 was the major isozyme in normal breast and fibrocystic disease, and in ductules derived from normal breast by collagenase digestion. One-fourth of the malignant tumors had a predominance of the mitochondrial form of MDH, while the cytosolic form predominated in all the normal and benign tissues. Acetylesterases A_4 and A_5 were low or absent in all the normal tissues, but were a major component of many of the tumor tissues, both malignant and benign. Butyrylesterase B_3 was a major component of most of the tissues examined, but was low in a few of the malignant tissues. No correlations of enzyme pattern with steroid receptors, clinical or pathological status were found.

Project Officer: D. Jane Taylor, Ph.D.
Program: Breast Cancer Diagnosis
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Animal and Human Mammary Tumors and Human Cell Culture Bank Facility

Principal Investigator: Dr. Arthur E. Bogden
Performing Organization: Mason Research Institute
City and State: Worcester, MA

Contract Number: NO1-CB-74175
Starting Date: 6/28/79 Expiration Date: 6/27/81

Goal: To function as a service facility for the cryopreservation, storage, and distribution of biologically characterized and monitored (a) animal and human mammary and endocrine related tumors transplantable in vivo, and (b) cell lines of human and animal breast tumor origin established in in vitro culture, for use by the Breast Cancer Task Force and other selected investigators.

Approach: Cryopreservation of mammary and endocrine related tumors of animal and human origin, as well as human breast tumor cell lines: (a) submittal of tumors and cell lines by qualified investigators able to furnish pertinent background information; (b) biological characterization of transplantable tissues, both pre- and post-cryopreservation, by determination of growth curves, specific effects on host organs, host (syngeneic and xenogeneic) survival, serum hormone levels, histology, karyology, response to ablative procedures; (c) cell lines tested for viability, plating efficiency, freedom from contamination and tumorigenicity by nude mouse implantation; (d) characterized tissue and cell lines preserved in Linde liquid nitrogen freezers according to well recognized, proven procedures.

Progress: During the period December 1, 1979 to December 1, 1980, 184 tumors were shipped to 91 investigators; 41% were of mammary and 8% of anterior pituitary origin. Two new tumors were received for cryopreservation and characterization and 9 human tumors (non-breast) were transferred to the DCT Tumor Bank. Breast tumor cell lines DU4475 and MDA-MB-436 have been established as transplantable solid tumor systems in athymic nudes. There is a current inventory of 252 transplantable tumors or sublines stored in 5,130 ampules in liquid N_2. Eight shipments of human and rat α-lactalbumin and/or specific antisera have been made. Anti-Type I, II and III collagen antiserum was received and is now also available for distribution. Current inventory of cell lines in cryopreservation in the in vitro cell bank includes 20 human breast tumors, 4 human normal epithelial, and 2 mouse and 1 rat mammary tumors. One hundred and eight shipments, which included 14 frozen ampules and 410 viable cultures, were made to 74 different laboratories, 16 of which were in foreign countries. During the past year there has been a 23% increase in shipments of in vivo animal tumor systems and a 74% increase in shipments of in vitro human cell lines. A bibliography relative to the transplantable tumors is being distributed upon request.

Project Officers: Chester V. Piczak, B.S., D. Jane Taylor, Ph.D.
Program: Breast Cancer Experimental Biology
FY 81 Funds: $148,500

CONTRACT RESEARCH SUMMARY

Title: Data Research Analysis for Breast Cancer Treatment Program

Principal Investigator: Ms. Marlene Dunsmore
Performing Organization: Mason Research Institute
City and State: Rockville, MD

Contract Number: NO1-CB-74140
Starting Date: 3/21/77 Expiration Date: 3/20/81

Goal: To increase the usefulness of data produced in projects related to the treatment of human breast cancer.

Approach: A central data file has been developed for three areas of study: (1) surgical adjuvant therapy; (2) tumor markers; and (3) estrogen receptor assays. The file allows comparisons of the results from various studies and provides a data base from which material can be quickly and conveniently retrieved. This data file is also implemented for testing new ideas, identifying groups of patients suitable for more detailed study, and for preparing reports to the medical community and the general public. The file is not intended to duplicate those at individual institutions but to perform analyses that are not possible at the individual institutions.

Progress: Mason personnel have designed a data collection and editing system for the Breast Cancer Studies Data Center. Clinical information is abstracted and entered via an IBM on-line disk file. The main file update system modifies clinical history files with new information and continues to edit for data consistency. Data concerned with treatment, histopathology, survival, and estrogen receptor status have been stored on 2,804 patients. Personnel have prepared extensive tabulations of these data for general meetings of the Breast Cancer Task Force Committee. They have sent each participating institution an analysis of its own data and of the collated information.

In February 1978 work was begun in support of the Biological Markers Project. The basic data collection and editing systems are operative. Background and clinical data have been gathered on 14,349 patients from three institutions. Mayo Clinic is serving as the repository for the serum samples. Benign tumor and metastatic cancer follow-up information is now being gathered. Research investigators have so far requested 8 shipments of serum specimens to test specific blood markers. Their laboratory results are being returned to the Data Center for evaluation.

Project Officers: Mary E. Sears, M.D., Ihor J. Masnyk, Ph.D.
Program: Breast Cancer Treatment
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: The Relationship Between Thyroid Disease and Breast Cancer

Principal Investigator: Dr. Farahe Maloof
Performing Organization: Massachusetts General Hospital
City and State: Boston, MA

Contract Number: NO1-CB-84230
Starting Date: 9/30/78 Expiration Date: 9/29/82

Goal: To examine the possible association of breast cancer with prior thyroid dysfunction.

Approach: This is a retrospective cohort study designed to measure the rates of breast cancer in women with and without prior thyroid disease. A mortality study will follow 7,000 women with thyroid disease seen at the Thyroid Clinic of the Massachusetts General Hospital between 1925 and 1975, and 7,000 matched population controls; 2,000 women seen at the Clinic but without identified thyroid disease will also be followed. Rates will be compared in women with various types of thyroid disease. A morbidity study will follow 1,600 women with previous thyrotoxicosis; this will include 500 women who became hypothyroid following the treatment and 500 who did not. Rates of breast disease will be compared according to mode of treatment as well as externally compared with rates from the Connecticut Tumor Registry.

Progress: Mortality Study: The card file of patients treated at the Thyroid Clinic was reviewed. From the 45,000 names, 13,400 women satisfied the study criteria, almost twice as many women as had been anticipated, allowing us to increase the sample size. This included 3,140 women with no thyroid disease. Pertinent medical data and follow-up information have been abstracted from the medical records of 9,600 of these women. One control woman was sought from the available Massachusetts Residents' List for each thyroid patient who resided in the state at the time of diagnosis; 10,200 women who resided in the same neighborhood and who were within two years of age of the case were selected. The information present in the Resident's List was abstracted, keypunched, and entered into the computer for each control woman selected. We recently began the follow-up search of the Massachusetts death certificates. So far, 913 deceased women have been found. As each death certificate is located, a form noting the date and cause of death is completed.

Morbidity Study: A computerized roster of the 1,955 women in the USPHS Thyrotoxicosis Follow-Up Study has been compiled. A search of the Massachusetts death certificates found 389 deaths. A questionnaire was mailed to 1,566 women on April 2, 1979. A second mailing to those who did not respond went out May 28, 1979. To date, 81% of the 1,955 women have been found dead or have returned a completed questionnaire. Those who have not yet responded are being traced through the medical records, telephone books, and Residents' Lists. The scheduling and supervision of the clinical examinations have begun. A special form to record the results of the physical examination and laboratory tests has been designed. So far, 490 patients have been examined.

Project Officers: Elizabeth P. Anderson, Ph.D., Bruce Nisula, M.D.
Program: Breast Cancer Epidemiology
FY 81 Funds: $78,500

CONTRACT RESEARCH SUMMARY

Title: Surgical Adjuvant Chemotherapy in Patients with Breast Cancer

Principal Investigator: Dr. David L. Ahmann
Performing Organization: Mayo Foundation
City and State: Rochester, MN

Contract Number: NO1-CB-33899
Starting Date: 6/30/73 Expiration Date: 6/29/81

Goal: To assess the effects of surgical adjuvant chemotherapy with or without radiation therapy in patients with operable but prognostically unfavorable breast cancer.

Approach: Patients with unfavorable breast cancer (node + or unfavorable signs) are assigned to treatment programs involving mastectomy followed by adjuvant chemotherapy with or without radiation therapy. The three treatment arms are a) L-PAM, b) CFP and c) CFP with radiation therapy. Because of the therapeutic disadvantage to L-PAM in the premenopausal setting, this treatment arm was dropped for this group of patients. The adjuvant chemotherapy was initiated up to six weeks in the postoperative period and when radiation is given it is given concomitantly with the chemotherapy. Chemotherapy programs are continued for a total of ten cycles or upon the appearance of recurrent disease, whichever should occur first.

Progress: The results of these three treatments have been assessed in 293 patients, 81 treated with L-PAM, 104 with CFP and 108 with CFP plus radiation therapy. Of these patients, 13 (4.4%) withdrew from treatment prior to completing the planned ten courses. A total of 211 patients have completed two or more years of survival followup. With respect to the premenopausal group of patients, L-PAM was found to be distinctly inferior to the utilization of CFP with or without radiation therapy as a treatment modality expressed both by disease-free interval and survival. In the postmenopausal group of patients thus far, none of the treatments employed have displayed a distinct advantage with respect to disease-free interval or survival. Specifically, virtually all patients experienced some degree of myelosuppression and no dose response or myelosuppressive effect was found to be influential on the disease-free interval or survival with the treatment program employed in this study. The dominant site of recurrent disease at the time of initial recurrence, however, does show that local and regional control was markedly improved with the addition of radiation therapy. Toxicities encountered were comparable except for unique toxicities exclusively associated with radiation therapy including radiation pneumonitis, esophagitis, pericarditis, radionecrosis and brachial plexopathy. The major morbidity encountered, however, in this group was in one patient necessitating hospitalization for radiation pneumonitis and two patients undergoing pericardiectomy for pericarditis, and one patient with a moderately severe plexopathy. Lymphedema was also observed about twice as commonly and was about twice as severe in the radiation treatment group.

Project Officer: Mary E. Sears, M.D.
Program: Breast Cancer Treatment
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: NCI Sera Bank Facility for the Breast Cancer Task Force

Principal Investigator: Dr. Vay Liang W. Go
Performing Organization: Mayo Foundation
City and State: Rochester, MN

Contract Number: NO1-CB-84296
Starting Date: 9/1/77 Expiration Date: 8/31/82

Goal: To establish and maintain a storage facility for serum specimens to be used by the Breast Cancer Task Force in a program designed to search for biological markers in breast cancer.

Approach: Sera specimens will be secured from breast cancer patients, benign disease patients, controls, and a screening population under separate contracts setting up a patient resource. The material will be processed, recorded and stored in -70°C deep freezers under easily retrievable conditions with all clinical data available. The sera will be used in the search for and verification of new breast cancer markers.

Progress: Collection and inventory methods have been developed. A special vial has been obtained and supplied to the collection areas. An operational shipping schedule has been established on a regular basis. Samples have been catalogued and systematically stored. Inventory during the forty-fourth month of the projects is listed:

Inventory Status April 1981	No. Patients	No. Vials
Screening Project (Columbia, MO)	11,379	122,080
Operative Patients (Grand Rapids, MI)	2,978	32,253
Operative Patients (Wilmington, DE)	575	5,917
TOTAL:	14,932	160,250

Collected Since April 1980	No. Patients	No. Vials
Screening Project (Columbia, MO)	1,837	19,119
Operative Patients (Grand Rapids, MI)	1,077	12,445
Operative Patients (Wilmington, DE)	93	1,009
TOTAL:	3,007	32,573

Since June 4, 1979, 8 coded serum panels have been shipped to investigators for evaluation of new breast cancer markers.

No. Patients	No. Vials
683	717

Project Officers: Ihor J. Masnyk, Ph.D., Mary E. Sears, M.D.
Program: Breast Cancer Treatment
FY 81 Funds: $100,000

CONTRACT RESEARCH SUMMARY

Title: Prognostic Factors for Disseminated Cancer in Patients with Early Breast Cancer

Principal Investigator: Dr. Paul Peter Rosen
Performing Organization: Memorial Hospital
City and State: New York, NY

Contract Number: N01-CB-74097
Starting Date: 8/1/77 Expiration Date: 7/31/81

Goal: To determine the frequency of subsequent metastatic breast cancer in a group of females with "early" invasive carcinoma and to identify those clinical and/or pathologic features or groups of features that are indicators of a high or low risk for dissemination of carcinoma.

Approach: A study population of 250 women with primary infiltrating breast carcinomas 1.0-2.0 cm in diameter, and a subset of 100 women with malignant tumors 1 cm or less in diameter will be identified in a retrospective study (1964-1969). These patients will have been treated by at least a modified radical mastectomy and have been found to have negative lymph nodes. The relationships observed between pathologic and clinical data and survival will be evaluated. Patients with primary tumors 2 cm or less with positive lymph nodes will also be studied to provide a basis for comparing the distribution of various features.

Progress: A 10-year follow-up study of 382 women with Stage I ($T_1N_oM_o$) breast carcinoma revealed recurrence and/or death due to cancer in 16%. Among 134 patients (35%) with a primary tumor 1.0 cm or less in diameter (Group A), 7% had recurrence and 5% died of breast carcinoma. Recurrences were observed in 21% of the 248 women with a tumor 1.1 to 2.0 cm in diameter (Group B) and 15% died of disease. These differences in recurrence and mortality were statistically significant. All recurrences were due to infiltrating duct or lobular carcinoma which accounted for 91% of the 382 carcinomas. Most strongly linked to recurrence was the finding of tumor emboli in lymphatics of the breast. This was found in 23 Group B patients and 10 of them (43%) died of disease. No recurrences were observed among the 7 Group A patients with lymphatic emboli. Other features associated with a significantly increased risk of recurrence were poorly differentiated carcinoma, marked lymphoid reaction to tumor, and menarche before age 12 or after age 14. No combination of variables proved to identify a subset of patients with an especially increased or low risk of recurrence. Stage I patients with lymphatic tumor emboli in the breast surrounding a carcinoma 1.1 to 2.0 cm in diameter have a sufficient risk for recurrence to warrant consideration of adjuvant systemic therapy. A very low risk of recurrence was observed for the following: any tumor 1.0 cm or smaller; and tubular, medullary or colloid carcinoma up to 2.0 cm. Analysis of 142 $T_1N_1M_o$ patients is currently under way.

Project Officers: D. Jane Taylor, Ph.D., Donald E. Henson, M.D.
Program: Breast Cancer Diagnosis
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Longitudinal Studies of Biologic Markers in Breast Cancer Patients

Principal Investigator: Dr. Morton K. Schwartz
Performing Organization: Memorial Hospital
City and State: New York, NY

Contract Number: NO1-CB-74206
Starting Date: 8/1/77 Expiration Date: 7/30/82

Goal: To assay human breast cancer tissue and sera prior to mastectomy and throughout the clinical course of the disease for potential markers, to determine how effective such markers would be for early detection of breast cancer and its recurrence, and to gain an understanding of the relationship between the concentration of the marker substances in the individual tumor and in the serum levels of the host.

Approach: Serum and tissue specimens from patients entering for diagnosis and for primary therapy are assayed for carcinoembryonic antigen (CEA), sialyltransferase, phosphohexose isomerase (PHI), spermine, ferritin, lactic dehydrogenase (LDH) and its isoenzymes, ß-hCG, γ-glutamyltranspeptidase (γ-GTP), α-fetoprotein and IgA. In tissue alone hormone receptors, total protein, DNA and glucose-6-phosphate dehydrogenase and measured and in serum aspartate aminotransferase (GOT), alkaline phosphatase, calcium and albumin. Serum specimens are collected prior to surgery, before discharge and then sequentially every 3 months the first year and every 6 months thereafter. The tissue is a portion of that obtained for hormone receptor assay at the time of biopsy or mastectomy. Tissue and serum biochemical data are compared and changes and differences related to the clinical course of the patient as well as demographic and pathology findings.

Progress: As of December 1, 1980, 393 patients had been entered into the study and additional patient accrual was terminated. Collection of serum specimens and their assay continues. There have been 56 patients in whom clinical recurrence has been observed. In some of these serum marker elevations preceded the clinical observation. However, there were also patients with recurrence in whom marker changes were not observed. The statistical technique of logistic regression is being used in an attempt to develop a multivariate model to predict recurrence from the initial tissue and pre-surgical blood data as well as other variables including nodal status and tumor size.

Project Officer: D. Jane Taylor, Ph.D.
Program: Breast Cancer Diagnosis
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Metabolism of Polycyclic Aromatic Hydrocarbons in the Induction of Mammary Tumor

Principal Investigator: Dr. A. Monaem El-hawari
Performing Organization: Midwest Research Institute
City and State: Kansas City, MO

Contract Number: NO1-CB-84227
Starting Date: 9/1/79 Expiration Date: 8/31/81

Goal: To determine whether differences in the disposition, metabolism, and macromolecular binding are related to differences in mammary tumor incidence caused by polycyclic aromatic hydrocarbons.

Approach: Carcinogenesis studies are being performed in sexually mature female rats (50 day-old) from Sprague-Dawley (SD), Long-Evans (LE) and Wistar-Lewis (WL) strains treated with single doses of MC or DMBA. The disposition, metabolism and DNA binding of these and other related carcinogens were studied in female rats of the 3 strains, in male SD rats and in younger (30 day-old), older (110 day-old), pregnant and lactating SD rats.

Progress: After treatment with both carcinogens, WL rats showed the highest susceptibility. Tumors were induced readily in SD rats while LE rats were the least susceptible. DMBA was more effective than MC as a mammary tumor inducer in the 3 strains. Most tumors induced in the WL and SD rats were malignant while LE rats developed mainly benign tumors. Disposition studies showed no major differences among the 3 strains in the mammary uptake of both carcinogens. A slower rate of clearance was found in the LE rats but the metabolic profiles were not different from the other strains. Mammary microsomes metabolized MC, DMBA and BaP to a variety of oxidative products. Also, freshly isolated mammary cells were active in converting these compounds to ethyl acetate- and water-soluble metabolites which included both K-region and non-K-region dihydrodiols. HPLC metabolic profiles from mammary cells differed from those of liver cells and subcellular fractions. Also, mammary enzymes catalyzed the conversion of the 3 hydrocarbons to metabolites that reacted with exogenous DNA. Binding was modified by inducers and inhibitors and was highest to DMBA followed by MC and BaP. This correlates with the carcinogenic potency of the 3 hydrocarbons. MC and DMBA binding to exogenous DNA was highest when catalyzed by mammary microsomes from 30 day-old rats. This contrasted with the in vivo findings in which binding to mammary DNA was highest in the 50 day-old animals.

Project Officer: Chester V. Piczak, B.S.
Program: Breast Cancer Experimental Biology
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Lipid Levels and Cholesterol Metabolism in Relation to Human Breast Cancer Risk

Principal Investigator: Dr. Angelos E. Papatestas
Performing Organization: Mount Sinai Medical Center
City and State: New York, NY

Contract Number: NO1-CB-84318
Starting Date: 9/30/78 Expiration Date: 9/29/82

Goal: To evaluate whether dietary or metabolic factors influence breast cancer risk by inducing systemic and/or local changes at the target organ affecting host's resistance.

Approach: Matched case-control study. Matching criteria: age, ethnicity, menopausal status. Data on past medical and family history, weight, obesity, dietary habits, serum lipids, fecal steroid metabolites, tissue cholesterol and fatty acids and case-control differences in these variables are evaluated. Correlation between these parameters and known risk factors, or tumor characteristics (tumor stage, presence of hormone receptors) are examined.

Progress: Significant differences between cases and controls were noted in:

VARIABLES	# OF PAIRS	CONTROLS	CASES	MEAN DIFFERENCE	PAIRED T-TEST	P
Serum						
Cholesterol (mg/dl) (CHOL)	140	193±36	204±40	-11±47	2.71	<0.01
CHOL Postmenopausal Women	49	202±37	226±35	-24±46	3.71	<0.001
Triglycerides (mg/dl)	135	99±63	119±67	-20±86	2.71	<0.01
Free fatty acids (mEq/L)*	74	.30±.12	.35±.15	-.05±.17	2.49	<0.025
Fecal Specimens						
Total steroids	39	44±31	61±36	-17±47	2.18	<0.05
Neutral steroids	39	29±23	43±29	-14±37	2.14	<0.05
% Cholesterol degraded	39	52±32	68±21	-16±39	2.58	<0.02
Dietary Intake						
% of calories from MFA**	11	16±3	12±4	+4±6	2.26	<0.05

*Premenopausal women **Monounsaturated fatty acids

These differences were present both in matched pairs of cases to controls with benign breast disease and pairs of cases to controls without benign breast disease. The magnitude of the differences varied in relation to ethnicity and menopausal status. The findings that serum lipids and fecal steroid metabolites are higher in cases compared to controls may partly reflect the observed differences in the type of dietary fat intake. Other factors (physical activity, psychosocial stress) affecting serum levels need further investigation. As tumor load increases did not correlate with lipid levels the observed differences probably precede rather than follow the appearance of breast cancer.

Project Officers: Elizabeth P. Anderson, Ph.D., Kenneth Lippel, Ph.D.
Program: Breast Cancer Epidemiology
FY 81 Funds: $80,000

CONTRACT RESEARCH SUMMARY

Title: Interrelationships Among Diet, Steroid Hormone Metabolism, and Human Breast Cancer

Principal Investigator: Dr. Marvin A. Kirschner
Performing Organization: Newark Beth Israel Medical Center
City and State: Newark, NJ

Contract Number: NO1-CB-84229
Starting Date: 9/30/78 Expiration Date: 9/29/81

Goal: To investigate steroid hormone production rates and metabolism in relation to obesity and dietary patterns.

Approach: This will be an in-depth study of androgen, estrogen and cortisol production, metabolism, and excretion in a cohort of 40 obese women undergoing drastic weight reduction and diet manipulation. The women will be studied prior to weight loss, after weight loss and stabilization on a high protein, low fat diet, and after isocaloric exchange to a more typical high carbohydrate, high fat diet. Values will be compared under three sets of conditions and further compared with those in lean, age-matched controls.

Progress: Baseline studies have been performed in 54 obese and 32 normal women, of which 34 and 22, respectively, have been worked up.

	Obese	Normal Controls	p Value
MCR Androstenedione (Δ)	3143 L/day	2140	<0.001
Plasma Δ Production Rate	3.53 mg/day	2.38	<0.05
Conversion $\Delta \rightarrow E_1$	2.17%	1.51%	<0.05
Conversion $\Delta \rightarrow$ Testosterone	7.59%	12.14%	<0.05
Urinary E_1 Prod. Rate	139.0 μg/day	98	<0.05

These data demonstrate increased clearance and production rates of Δ, as well as altered metabolism of Δ to both testosterone and E_1. Urinary E_1 production rates are elevated in obese women, due largely to increased extragonadal metabolism of Δ to E_1. To date, 32 normal volunteers have been studied during normal diet, high protein diet and high carbohydrate diet. Analyses of basal dietary patterns (previous week recall) showed no major differences in control vs obese women, except in total caloric consumption. Hormonal studies reveal no significant differences in Δ and E_1 production, and peripheral metabolism on these differing diets. Our major problems continue to be a) high patient drop-out prior to weight loss to ideal weight, and b) instability of weight once basal levels are reached, requiring longer periods of stabilization prior to repeat studies.

Project Officers: Elizabeth P. Anderson, Ph.D., Lynn Loriaux, M.D.
Program: Breast Cancer Epidemiology
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Relation of Intestinal Flora to Breast Cancer in Humans

Principal Investigator: Dr. Sherwood L. Gorbach
Performing Organization: New England Medical Center
City and State: Boston, MA

Contract Number: NO1-CB-74104
Starting Date: 7/1/77 Expiration Date: 12/31/80

Goal: To determine the influence of dietary factors on the metabolism of estrogens by bacteria in the large bowel.

Approach: The estrogen profiles are determined in the serum, urine, and feces of young and older women eating "Western" or vegetarian diets and in women with a history of breast cancer. In addition, serum SHBG and prolactin are being determined. Novel fecal metabolic transformation of estrogens and the possible role of these transformations in the etiology of breast cancer are being investigated.

Progress: The total of 54 subjects in 5 groups have completed four 72-hour collections of urine, feces, and dietary records plus 3 daily blood samples within a one-year period. The laboratory analysis of all the samples has been completed and statistical analysis is now being completed. The main conditions being analyzed are ovarian state (young menstruating women versus postmenopausal women) and diet (vegetarian versus omnivores). A fifth group of postmenopausal subjects with breast cancer has also been studied. Analysis of the dietary data indicates that the young omnivores consume 41.1% of their calories as fat and the old vegetarians 30.2% of their calories as fat. Protein intake is similar but dietary fiber is higher in the vegetarian, approximately 30 g a day versus 12-18 g a day in the omnivores. Analysis of the dietary records includes 27 separate nutrients with comparison of means as well as the analysis of variation within each group. The fecal data indicate that vegetarians have almost a two-fold increase in wet and dry fecal weight. Sex hormone binding globulin was analyzed in the serum and showed that the breast cancer group had half the level of the other four groups. In contrast, morning and mid-day serum prolactin determinations showed no difference between groups. The data on estrogen levels in plasma, urine, and feces are in the process of being analyzed. Fecal excretion of conjugated estrogens is increased 2-3-fold in vegetarians and the urinary excretion of estriol-3-glucuronide is higher in omnivores. This result further supports the other findings that omnivores absorb more estrogens from the intestinal tract.

Project Officers: Elizabeth P. Anderson, Ph.D., Carl Smith, Ph.D.
Program: Breast Cancer Epidemiology
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Produce and Identify Antibodies to Collagens/Procollagens and/or Related Enzymes

Principal Investigator: Dr. Burton Goldberg
Performing Organization: New York University Medical Center
City and State: New York, NY

Contract Number: NO1-CB-84314
Starting Date: 9/1/78 Expiration Date: 8/31/81

Goal: To produce specific antibodies to the carboxyterminal nonhelical sequences of human type I procollagen in sufficient quantities for storage and distribution to other investigators.

Approach: Culture human skin fibroblasts (CRL1121) in roller bottles and isolate the procollagen in the culture medium, then subject it to specific bacterial collagenase digestion. Purify the carboxyterminal fragment by ion exchange chromatography, then produce antibodies in appropriate animal species (rabbit, goat, sheep). Purify the antisera by absorption techniques and/or affinity chromatography and confirm their specificity by Ouchterlony technique, immunoelectrophoresis, passive hemagglutination, and radioimmunoassay.

Progress: To date 120 liters of medium from confluent cultures of human skin fibroblasts were obtained. Approximately 1 gram of procollagen-enriched lyophilate was harvested and a portion was subjected to collagenase digestion to generate the non-helical carboxyterminal propeptide fragment from procollagen. The propeptide fragment was purified by ion exchange chromatography on DEAE-cellulose and 50 mg of the pure protein was prepared. One sheep and 7 rabbits were immunized with the preparation. Some rabbit antisera have titers as high as 1/80,000 and sheep antisera have titers 1/10,000 to 1/14,000 by radioimmunoassay. A new immunization protocol raised the titers to 1/40,000. Affinity purified IgG (3.5 mg) was recovered from 30 ml of rabbit antiserum which had an original titer of 1/60,000. The purified IgG reacts specifically with the propeptide antigen and lacks cross-reactivity for native human collagen. IgG gives strong and specific indirect immunofluorescence with cultured human fibroblasts when used at a concentration of 2.8 μg/ml.

Presently, the stocks of affinity-purified IgG are as follows: 25 ml of rabbit IgG at a concentration of 142 μg/ml in PBS and 10 ml of sheep IgG at a concentration of 142 μg/ml in PBS. In the current year plans are to at least double the amounts of affinity-purified antibodies on hand and to run additional tests of their specificity for the carboxyterminal propeptides of type I human procollagen.

Project Officer: Chester V. Piczak, B.S.
Program: Breast Cancer Experimental Biology
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Epidemiology of Minimal Breast Cancer in Initially Asymptomatic Women

Principal Investigator: Dr. Bernard S. Pasternack
Performing Organization: New York University Medical Center
City and State: New York, NY

Contract Number: NO1-CB-74103
Starting Date: 7/15/77 Expiration Date: 6/30/81

Goal: Investigate by means of risk factor analysis whether minimal breast cancer in initially asymptomatic women is essentially different from clinical breast cancer or whether it is an early manifestation of the same disease; identify risk factors associated with tumor aggressiveness.

Approach: We have obtained and will analyze demographic and medical data recorded at the Guttman Breast Diagnostic Institute, which since 1968 has been offering free breast examinations to women living in New York City. The study group will consist of an estimated 874 valid cases out of a total of 1,386 detected through November 21, 1979, and approximately 2,168 valid controls out of a random selection of 2,700. After exclusions due to symptomaticity, 478 cases and 1,712 controls will remain. Two independent histopathologic diagnoses are being performed; one at New York University Medical Center (NYU) and the other at Saint Barnabas Medical Center (SB). Cases will be compared according to three tumor criteria: a) level of invasiveness, b) level of aggressiveness, and c) histologic type. Comparison of all cases to controls should result in estimates of relative risk within the range found at other screening centers, whereas the comparison of clinical cases to controls should provide estimates within the same order of magnitude as registry data.

Progress: Protocols have been established for all phases of the study: collection of demographic and screening data, pathology review, and mammography review. Basic identification forms have been coded, keypunched, and filed for all 1,386 cases, and 2,594 controls. Examination code forms for about 3,980 participants have been coded, keypunched, and filed. Initial and recall histories have been coded, keypunched, and filed for about 3,850 participants. Pathology material has been requested for 813 cases and received for 625 (76.9%). Material for 58 cases is definitely unavailable, due to closed hospitals and lost slides, and for 45 cases will not be requested due to prior mastectomy. Six hundred fifty-eight cases remain outstanding. Mammography review has been performed for 417 cases and 87 controls, the NYU pathology review for 538 cases, and the SB pathology review as well for 529 cases. Of those for which two reviews have been completed, the initial rate of consensus is 69.2%. Consensus review has been able so far to resolve all remaining differences. Identification of inconsistencies in the data by means of specifically designed computer programs is being performed for the 19,540 data records computerized thus far. These inconsistencies are being resolved by examination of participants' files at both NYU and the Guttman Institute.

Project Officers: Elizabeth P. Anderson, Ph.D., Benjamin Hankey, Sc.D.
Program: Breast Cancer Epidemiology
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Development of an Assay for Genetic Damage to Mammary Gland Cells

Principal Investigator: Dr. Steven D'Ambrosio
Performing Organization: Ohio State University
City and State: Columbus, OH

Contract Number: NO1-CB-84226
Starting Date: 9/1/78 Expiration Date: 8/31/81

Goal: To develop an inexpensive, rapid, and quantitative assay for detecting genetic damage and its repair in mammary cells in vivo following exposure to carcinogenic agents.

Approach: Measure DNA damage directly by an assay using S_1 endonuclease. Determine changes in the size of nonradiolabeled DNA resulting from endonuclease treatment using alkaline or neutral sucrose gradient sedimentation. After sedimentation, the nonradiolabeled DNA will be quantitated by a spectrofluorometric technique. Quantitate the mammary epithelial cell DNA damage by double label autoradiography. DMBA sensitive and resistant rat strains and noncarcinogenic and less carcinogenic analogs, 2-FL-DMBA and 5-FL-DMBA, will be used for these studies.

Progress: Since the inception of the contract this laboratory has: a) developed techniques for the isolation of mammary nuclei essentially free of contaminating lipids; b) developed a technique that permits sedimentation and detection of nanogram quantities of nonradiolabeled mammary DNA; c) quantitated the molecular weight of such DNA (determination of the number of breaks induced); d) synthesized DMBA and its fluorinated analogs and ENU; e) developed methods for separation and purification of these cold and radiolabeled compounds; f) quantitated the number of DNA-carcinogen adducts produced in mammary gland and compared it to that produced in other tissues; g) determined the level of urinary metabolites produced by radioactive and nonradioactive DMBA and its fluorinated analogs and h) begun to correlate the types and quantities of damage to the carcinogenic potential of the compounds tested.

These studies have led to the development of an inexpensive, rapid and quantitative assay for detecting in vivo genetic damage of mammary gland cells. Further experiments are in progress and should be completed during year three of this contract to determine not only the amount of DNA damage induced but also to correlate the rate of removal with the tumor susceptibility of carcinogen and noncarcinogen compounds tested as a function of both rat strain, dose, age and location of mammary gland.

Project Officer: Chester V. Piczak, B.S.
Program: Breast Cancer Experimental Biology
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Suppression of Endocrine Function by Systemic Agents for Breast Cancer Therapy

Principal Investigator: Dr. Richard J. Santen
Performing Organization: Pennsylvania State University
City and State: Hershey, PA

Contract Number: NO1-CB-53851
Starting Date: 5/15/75 Expiration Date: 5/14/82

Goal: To produce suppression of endocrine function with aminoglutethimide (AG), to establish the mechanism of steroid inhibition, and to compare the effects of surgical adrenalectomy, antiestrogen therapy, and aminoglutethimide in human breast carcinoma.

Approach: Female patients with inoperable, recurrent, or metastatic breast carcinoma and whose tumors are either estrogen receptor positive or unknown are selected for study. Women are randomized into two separate therapeutic trials: a comparison of medical adrenalectomy (AG + hydrocortisone) vs. surgical adrenalectomy, and of AG vs. the antiestrogen, tamoxifen. Extensive endocrine studies evaluate the effects of AG on extra-adrenal estrogen production, androgen, progestin, and prolactin secretion, and steroid metabolism.

Progress: Women with metastatic breast cancer are entered into protocols utilizing surgical adx, medical therapy with aminoglutethimide (AG) and tamoxifen (Tam). In a randomized trial of 96 patients, a 53% objective response rate to AG plus hydrocortisone (HC) and a 43% regression rate to surgical adx were observed. Medical treatment with AG and surgical adx produced a similar reduction of estrogen levels, whereas androgen secretion was preserved in the medical group. Four women treated initially with surgical adx experienced additional estrogen suppression upon addition of AG and in 2, partial objective tumor regression resulted. Systemic studies of adrenal reserve immediately after stopping AG revealed normalization of basal cortisol levels and return of stress responses within 72 hr. A randomized trial of AG-HC vs. the antiestrogen, tamoxifen, entered 61 patients. Forty-eight percent responded objectively to AG-HC and 42% to Tam (p = NS). However, bone lesions appeared more favorable to AG therapy (7/13 CR + PR = 54%) than to Tam (4/18 CR + PR = 22%). Cross-over responses to Tam in AG-HC-resistant patients occur infrequently but Tam-resistant women appear to have secondary responses to AG-HC. Hormonal levels in 147 AG-treated patients revealed equal estrogen suppression in objective responders as in patients with progressive disease but DHEA-S and androstenedione levels were higher during treatment in patients with progressive disease. Overall, these studies suggest that AG-HC is a logical alternative to surgical adx and produces clinical responses which probably differ from those induced by Tam.

Project Officer: Mary E. Sears, M.D.
Program: Breast Cancer Treatment
FY 81 Funds: $72,000

CONTRACT RESEARCH SUMMARY

Title: Prognostic Significance in Breast Cancer of Regional Lymph Node Immune Response

Principal Investigator: Dr. Susanna Cunningham-Rundles
Performing Organization: Sloan-Kettering Institute
City and State: New York, NY

Contract Number: NO1-CB-84228
Starting Date: 9/1/78 Expiration Date: 8/31/81

Goal: Evaluation of the relevance of regional lymph node immune response to prognosis in breast cancer. This will require an assessment of cell-mediated immune reactivity in well-standardized in vitro assays to defined antigens associated with the development of disease.

Approach: Immunological studies will be performed on lymph node cells of 100 patients with primary operable breast cancer, using a total of 4-6 lymph nodes per patient including both negative and positive nodes, ideally from each level (I-III). In addition, control lymph nodes will be obtained from 50 other patients. The assays to be done on both peripheral blood and lymph node mononuclear cells include leukocyte migration inhibition factor (LMIF) and lymphocyte transformation tests, the latter comprising PHA, Candida, E. coli, T-antigen and MuMTV. A third class of newer tests includes natural killer cells, suppressor cells, cell surface markers and monocyte function assays. Clinical and demographic data as well as histopathologic data on tumor size and histologic type will be obtained. Three-year follow-up information on recurrence and survival status will be recorded. Correlation of all factors will be statistically analyzed.

Progress: Principal findings are as follows: 30% of patients with breast cancer had reduced or negative NK activity of PBL toward K562 target cells. About 40% of patients with tumor positive nodes and 25% of patients with tumor negative nodes had negative PBL NK activity. Regional lymph node cells (RLNC) from 21% of patients had significant NK activity toward K562 in contrast to control RLNC including RLNC from patients with benign lesions where positive NK activity was not observed. Increased numbers of T_γ lymphocytes were found in 70% of patients' RLNC and 40% of PBL; these increases did not have a simple correlation with NK activity. Neither PBL nor RLNC were found to have suppressor cell activity in either autologous or allogeneic MLR. RLNC were markedly stronger as stimulating cells in MLR proliferative responses to mitogens, antigens and putative disease-related antigens were different in patients with tumor positive and negative nodes, suggesting tumor influence on RLNC activation.

Project Officers: D. Jane Taylor, Ph.D., Donald E. Henson, M.D.
Program: Breast Cancer Diagnosis
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Epidemiologic Characteristics of Medullary and Lobular Breast Cancer

Principal Investigator: Dr. Paul P. Rosen
Performing Organization: Sloan-Kettering Institute
City and State: New York, NY

Contract Number: NO1-CB-63997
Starting Date: 6/30/76 Expiration Date: 12/29/80

Goal: To identify and describe morphologic features of human female mammary carcinoma which are significantly related to known risk factors for the development of such carcinomas.

Approach: Detailed epidemiologic information was obtained by interviews from women with mammary carcinoma and correlated with pathologic features of the tumors. The analysis of the data emphasized comparison of medullary and lobular carcinoma with duct carcinoma.

Progress: A total of 1,227 patients have been accessioned into the study. Among the cases reviewed, 81 women were found to have only medullary carcinoma, 38 only in situ lobular carcinoma, and 59 only infiltrating lobular carcinoma. In addition, 42 patients had lobular carcinoma (38 invasive, 4 noninvasive) combined with another type of carcinoma, and 11 patients had medullary carcinoma associated with another type of carcinoma. Interviews have been conducted with 98% of the patients.

Patients with medullary carcinoma had a significantly lower mean age at diagnosis than those with duct and lobular carcinoma. There was a disproportionately high number of non-whites in the medullary carcinoma group. A secondary correlation with medullary carcinoma was a higher frequency of birth in the southern part of the United States as well as in South and Central America. The number of Oriental women was too small for analysis. Patients with medullary carcinoma tended to weigh more at diagnosis than those with other types of carcinoma, but the differences were not significant when evaluated in terms of age and optimum weight. No correlation between height or height-weight indices and tumor type was observed. Preliminary analysis of methods of clinical examination indicates significant relationships between the frequency of physician and mammographic examination and tumor stage. No correlation between frequency of self-examination and tumor histology has been found. Overall, 32% of patients had at least one female relative treated for breast cancer, ranging from 29% for patients with infiltrating duct carcinoma to 42% for those with lobular carcinoma in situ. There was a strong association of medullary carcinoma with positive maternal history of breast cancer while lobular carcinoma was associated with sister pedigrees.

Project Officers: Elizabeth P. Anderson, Ph.D., Roger Connelly
Program: Breast Cancer Epidemiology
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Biochemical Analysis of Human Breast Cyst Fluid (BCF)

Principal Investigator: Dr. Morton K. Schwartz
Performing Organization: Sloan-Kettering Institute
City and State: New York, NY

Contract Number: NO1-CB-53853
Starting Date: 6/30/75 Expiration Date: 9/14/82

Goal: To establish the biochemical and immunochemical composition of human BCF; to search for a marker which might be useful in understanding the formation of cysts, their treatment, and the risk of patients with cysts developing cancer.

Approach: BCF from patients with cystic mastopathy will be analyzed for polypeptide and steroid hormones, tumor-associated antigens, enzymes, lipids, minerals, and trace elements. These data will be correlated with each other and with the demographic information. Fluid will be analyzed from patients with recurrent cysts and clinical follow-up will be obtained on all patients.

Progress: Patient entry has been completed. There have been 1,044 patients (1,830 specimens) entered into the study. About 25% of the patients have had recurrent cysts and additional specimens submitted for analysis since their initial aspiration. As previously noted, the concentration in many BCF specimens of CEA, α-fetoprotein, ß-subunit hCG, calcium, copper, zinc, total protein, albumin, cholesterol, phosphohexose isomerase, γ-glutamyltranspeptidase, ß-glucuronidase, lactic dehydrogenase, amylase, dehydroisoandrosterone, androsterone, and their sulfates are many-fold the concentrations of these constituents found in serum. Correlation of BCF concentrations for many of these constituents in the same patients was found to be significant. The specimen variation was much less in specimens from the same patients obtained either at the same time or on subsequent aspiration than that from patient to patient. Notwithstanding the large BCF to serum gradient, isotope studies have indicated a flow influx and efflux of the steroids into the cyst fluid. The fluid appears to contain material both of a secretory nature and that resulting from cell breakdown. BCF contains low but detectable levels of terminal deoxynucleotidyl transferase (TdT) and DNA polymerases were observed in BCF and in supernatant from cells from BCF maintained in culture media. Preliminary biostatistical analysis has indicated that in the 40-65 years age group where the cyst occurrence is most prominent, the incidence of breast cancer in cyst patients is 625 per 100,000 as compared to 144 per 100,000 from estimates in normal women. Only follow-up of patients is continuing to determine the true incidence of breast cancer in cyst patients and to establish whether this incidence is related to the biochemical findings.

Project Officers: Bernice T. Radovich, Ph.D., R. Quentin Blackwell, Ph.D.
Program: Breast Cancer Diagnosis
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Growth and Passage of Primary Culture of Normal Mammary Epithelial Cells

Principal Investigator: Dr. Dayton S. Misfeldt
Performing Organization: Leland Stanford Jr. University
City and State: Stanford, CA

Contract Number: NO1-CB-74094
Starting Date: 7/1/77 Expiration Date: 6/30/81

Goal: To define conditions for the growth and passage of normal mammary epithelial cells in culture.

Approach: Conditions for growth and passage are determined by colony and cell count with an established mouse mammary cell line (NMUMG) and primary cultures of BALB/c mouse mammary gland.

Progress: Conditions for growth and passage of mammary epithelial cells must be considered in the context of a mixed cell population obtained during mammary gland dissociation. Differential stimulation of epithelial growth and fibroblast suppression has been investigated: 1) The addition of cholera toxin results in a 50% inhibition of fibroblast growth without suppression of epithelial growth. 2) Serum-derived plasma which attempts to remove the platelet-derived growth factor, a powerful stimulus for fibroblast growth, inhibits fibroblast growth to a greater extent than it inhibits epithelial growth. 3) Collagen as a culture substratum limits fibroblast overgrowth of the epithelial cell cultures. Eight epithelioid appearing clones have been isolated and passaged from primary mouse mammary tissue. However, chromosomal analysis of three has shown them to be aneuploid. The use of kidney epithelial feeder layers did not increase cloning efficiency of the Namru mammary cell line, so rat mammary epithelial cells are currently being tested as feeder cultures. If they increase Namru cloning, they will be used to obtain clones of primary mouse epithelial cells.

Project Officers: Chester V. Piczak, B.S., D. Jane Taylor, Ph.D.
Program: Breast Cancer Experimental Biology
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Longitudinal Studies of Biologic Markers in Breast Cancer Patients

Principal Investigator: Dr. Howard H. Sussman
Performing Organization: Stanford University School of Medicine
City and State: Stanford, CA

Contract Number: NO1-CB-74086
Starting Date: 8/1/77 Expiration Date: 7/30/82

Goal: To assay human breast cancer tissue and sera, prior to mastectomy and throughout the clinical course of the disease, for potential markers to determine how effective such markers would be for early detection of breast cancer and its recurrence, and to gain an understanding of the relationship between the concentration of the marker substances in the individual tumor and in the serum levels of the host.

Approach: Tumor and sera of patients presenting initially for diagnosis and primary therapy (Category 1) will be assayed for the fetoplacental proteins, i.e., placental alkaline phosphatase (PAP), human chorionic gonadotropin (hCG) α and β, and carcinoembryonic antigen (CEA); and tests on sera will be repeated sequentially every three months. Patients developing recurrences (Categories 2 and 3) will be included with a study population from the Northern California Oncology Group. Another objective of the study will be to identify new ectopically synthesized placental membrane proteins, which may be common to both trophoblasts and neoplastic breast tumor cells.

Progress: Serum assays have been continued on the 125 patients participating in the study. One patient from Category 1 has relapsed into Category 2. Three of her four marker levels increased, with two of these becoming abnormal, in the period of three to eight months prior to the diagnosis. The patient has since declined to be followed. A receptor specific for transferrin has been found in neoplastic breast tumors. Microsomes from these tumors demonstrate 11-35% binding of transferrin, while those from normal breast tissue show only 2-3% binding. A radioimmunoassay has been set up to detect the level of transferrin receptor on cell membranes. Preliminary results, expressed as μg receptor/mg protein, show normal breast (0.2) and a benign male breast (0.4) to have low levels, while placenta (33.6) has a high level. Eleven breast cancer tumors have been assayed and those levels fall between these two limits. Data on the 400 subjects from whom we have at least one blood sample, including controls, is continuing to be collected and entered into a computer for future evaluation.

Project Officers: D. Jane Taylor, Ph.D., Donald E. Henson, M.D.
Program: Breast Cancer Diagnosis
FY 81 Funds: $27,000

CONTRACT RESEARCH SUMMARY

Title: Morphological Properties of Normal and Abnormal Human and Rodent Mammary Tissue

Principal Investigator: Dr. Elinor Spring-Mills
Performing Organization: State University of New York
City and State: Syracuse, NY

Contract Number: NO1-CB-84239
Starting Date: 8/14/78 Expiration Date: 8/13/81

Goal: To evaluate structural differences among normal, dysplastic, and cancerous mammary glands.

Approach: To describe, quantitate, and compare certain morphological and functional characteristics of normal, hyperplastic, and carcinomatous human and mouse mammary glands in vivo and in vitro. Human tissues obtained at biopsy, mastectomy and reduction mammoplasty will be prepared for light microscopy (LM), transmission electron microscopy (TEM), scan electron microscopy (SEM), and quantitative electron microscopy (QEM) or morphometry. Animal tissue from nonpregnant (pubertal and adult), pregnant, and multiparous C3H mice will be studied.

Progress: During the past year, tumors and proliferative lesions from 40 women have been explanted and cultured. Survival has been poor to excellent in synthetic medium for 6-42 days. The effects of no hormones, insulin, hydrocortisone, prolactin, glutamine and vitamin A, alone and in combination, have been tested and evaluated at the light microscopy level. A large computer program is being written to analyze the interrelationships between the responses of the patient's tissues to the organ culture conditions, the pathological diagnosis of the breast lesion, the patient's zero time serum hormone levels for prolactin, progesterone, estrone and estradiol, and other risk factors. This program is to generate a model for testing the relationship of particular variables to the onset and subsequent course of certain breast diseases and the value of the culture systems for assessing tissue responsiveness to hormones, tissue potential for proliferation and growth, etc. A pilot immunocytochemical study of immunoreactive insulin in human breast tumors is under way.

The mouse project has been expanded because they found that morphologic alterations related to HAN and other lesions of undetermined biologic significance are appearing in the 2 1/2-3 month old C3H/HeJ mice. The breasts, ovaries, uteri, adrenals and oviducts from C3H/HeJ mice have been studied with the LM, SEM, and TEM. To better evaluate the data, parallel studies have been under way since April 1980 on C3HeB/FeJ mice which have low mammary tumor incidence.

Project Officer: Chester V. Piczak, B.S.
Program: Breast Cancer Experimental Biology
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Purification of Estrogen Receptor in Tangible Amounts

Principal Investigator: Dr. Giovanni Alfredo Puca
Performing Organization: Universita di Napoli
City and Country: Napoli, Italy

Contract Number: NO1-CB-64074
Starting Date: 9/30/76 Expiration Date: 5/29/81

Goal: To isolate and purify the "native" form of the estrogen receptor in milligram quantities.

Approach: Carry out large-scale tissue disintegration and centrifugation for isolation of estrogen receptor from calves' uteri. Purify the "native" form of estradiol receptor by a combination of affinity chromatography on new adsorbents and conventional separation methods.

Progress: The procedure for the purification of the native form of estradiol receptor of calf uterus and recently published (Journal of Steroid Biochemistry, 12, 105, 1980) was utilized with one modification to render the purification feasible when large volumes of cellular extract have to be handled. The tissue homogenate is now centrifuged in a refrigerated centrifuge because the capacity is much larger than the ultracentrifuges. The low speed supernatant is then incubated batchwise with heparin-agarose. After elution of the estradiol binding activity by heparin, the protein solution is then subjected to high speed centrifugation in an ultracentrifuge. Since the volume of this eluate is usually reduced to one tenth the volume of the original cellular extract, the ultracentrifugation step becomes much easier.

The immobilization of receptor on the estradiol containing derivative is carried out batchwise to shorten the time of incubation and to avoid loss of estradiol binding activity. The estradiol derivative is then packed in a column and washed very extensively with various cycles of low and high salt (2 M KCl) buffers. The receptor is eluted from the column in a very sharp peak with a buffer that contains, in addition to estradiol and chaotropic salt, 10% of dimethyl formamide. Sodium dodecyl sulfate polyacrylamide gel electrophoresis showed that, after these two simple affinity chromatography steps, receptor was at least 70% pure. Depending on the amount of the binding activity originally present in the extract, in the last three preparations 60, 96, and 380 μg of pure receptor starting from 450 gm of calf uteri was obtained.

Project Officers: Chester V. Piczak, B.S., D. Jane Taylor, Ph.D.
Program: Breast Cancer Experimental Biology
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Correlations Between Morphology and Epidemiology of Breast Cancer

Principal Investigator:	Dr. Björn Stenkvist
Performing Organization:	University Hospital, Uppsala
City and Country:	Uppsala, Sweden
Contract Number:	NO1-CB-53968
Starting Date:	6/30/75
Expiration Date:	6/30/81

Goal: To ascertain possible correlations between morphologic variables such as cytologic and histopathologic classifications and established epidemiological risk factors of breast cancer.

Approach: Within a clearly defined area and population (4 Swedish counties) 181 breast cancer cases occurred during a defined study period (5 months). From 179 of the patients both epidemiological and morphological data could be obtained. From 179 exactly age-matched controls epidemiological data were recorded in the same way. The tumors were characterized by computerized cytometry of the cell population in the tumors as well as by conventional morphology, resulting in an objective atypia measure.

Progress: In collaboration with Dr. Alan Morrison, Harvard School of Public Health, files of the epidemiologic and morphologic data have been established on the DEC-20 computer at the Sidney Farber Cancer Institute. Programs have been written to select subsets of this information for specific analyses. Preliminary analysis has been done to verify the programming and confirm the feasibility of the computational procedures. These analyses have involved both comparisons of suspected risk factors between cases and controls and comparisons of risk factors among groups of cases defined according to histologic characteristics. Detailed epidemiologic analysis of the data is beginning.

The patients have been followed up for the first four years postmastectomy. A "malignancy grade" for breast carcinomas has been developed, based on image analysis and pattern recognition. This measure of malignancy grade had a high prognostic significance and was applicable as an index of recurrence risk in each individual case.

Project Officer: Elizabeth P. Anderson, Ph.D.
Program: Breast Cancer Epidemiology
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Biologic Characterization of "Premalignant" Human Mammary Epithelial Hyperplasias

Principal Investigator: Dr. Hanne M. Jensen, M.D.
Performing Organization: University of California
City and State: Davis, CA

Contract Number: NO1-CB-84316
Starting Date: 9/18/78 Expiration Date: 9/17/81

Goal: To establish if angiogenesis is a reliable criterion for precancer of the human breast and to characterize by biochemical and immunological markers the type(s) of lesions that possess angiogenic capacity from those that do not.

Approach: Fresh, parenchymal structures and hyperplastic lesions stained with methylene blue chloride are isolated and studied for angiogenic potential by transplantation onto the iris of female rabbits. Six micron thick frozen sections of parts of isolated structures and lesions are stained with fluorescent labeled anti-human immunoglobulins G, A and M, to characterize them immunologically and with fluorescent labeled estrogen and progesterone to detect hormone receptors.

Progress: From 91 breast specimens 1,077 transplants derived from 784 structures and lesions were studied; 200 transplants became nonexperiments because they contained no epithelium or floated off the iris. Statistical evaluation indicated that 5 successful transplants from 5 different lesions from a given case were needed to prevent false negative data for angiogenesis. There were 409 successful transplants of normal and atypical lobules; 54 of 362 (15%) normal lobules were angiogenic. The frequency of angiogenesis was equal in cancer associated and noncancerous cases. Four of 23 (17%) atypical lobules from noncancerous biopsies were angiogenic. Fourteen of 23 (61%) atypical lobules from cancer associated breasts were angiogenic. The probability of the observed differences in angiogenic potential of atypical lobules occurring by chance is less than 0.01. A higher proportion of lobules from cancer cases were atypical [23 of 95 (24%)] than those from benign cases [23 of 314 (7%)]; chance probability is less than 0.0001. Atypical lobules were derived from 10 women with cancer. Nine of these had one or more angiogenic atypical lobules. Atypical lobules were obtained from eight women without cancer. Four of these had one or more atypical lobules that were angiogenic. The probability of this occurring by chance is greater than 0.05 but less than 0.1. Presumably these four women have greater risk for developing cancer at a later date. Most angiogenic atypical lobules secrete immunoglobulins and those found in women after age 60 appear strongly positive for estrogen receptors (ER) if indeed the fluorescent estrogen is specific. It is hypothesized that postmenopausally all hormone dependent tissues and lesions with low ER content regress due to lack of stimulation but those with high ER content persist.

Project Officers: D. Jane Taylor, Ph.D., Donald E. Henson, M.D.
Program: Breast Cancer Diagnosis
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Growth and Passage of Primary Cultures of Normal Mammary Epithelial Cells

Principal Investigator: Dr. Hideo Masui
Performing Organization: University of California
City and State: La Jolla, CA

Contract Number: NO1-CB-74188
Starting Date: 8/1/77 Expiration Date: 7/31/81

Goal: To isolate and maintain growth of pure normal mammary epithelial cells in culture.

Approach: Determine the hormonal and nutritional requirements of established animal and human mammary tumor cell lines. Proceed with similar studies on primary cultures of human mammary tumors obtained from autopsies and mastectomies. Determine the hormonal content, blood serum components, and growth factors (ovarian, nerve, epidermal, etc.) to prepare a defined media to maintain growth and passage of normal mammary epithelial cell lines.

Progress: Normal human mammary epithelial cells were supplied by Dr. Martha Stampfer which were obtained from reduction mammoplasty. The mammary tissue was treated with a digestion mixture of collagenase and hyaluronidase to release organoid structure-containing epithelial cells and myoepithelial cells. The organoids were collected by filtration and centrifugation and then cryopreserved in liquid nitrogen until use. These normal mammary epithelial cells have been grown in a complex medium which is a mixture of F12 and DME (1:1) supplemented with 5% fetal bovine serum, 4.5 g/L glucose, 5 μg/ml insulin, 5 μg/ml epidermal growth factor, 5 μg/ml cholera toxin, 5 x 10^{-10} M hydrocortisone, estradiol, dihydrotestosterone and triiodothyronine and then mixed with an equal volume of conditioned medium obtained from confluent cultures of human fetal epithelial cells from intestine or human adult bladder. One problem is that normal cells soon become senescent. Therefore, the supply of these cells is limited. Conditioned media from some human tumor cell lines have been used since tumor cell lines do not show senescence and the supply is unlimited. Various human tumor cell lines were established from heterotransplanted human tumors in athymic mice which include five colon carcinoma lines, four lung carcinoma cell lines, an astrocytoma and pheochromocytoma cell lines, and a mammary tumor cell line. All tumors were from different patients. These human tumor cells were grown to confluency and conditioned media were prepared to determine their effects on the growth of normal human mammary cells. The conditioned media from human colon carcinoma and human lung carcinoma cell lines seem to be satisfactory. These human carcinoma cell lines require a low concentration of serum (0.5%), when supplemented with hormones and factors; therefore, attempts will be made to eliminate serum completely. Factors in the serum-free conditioned media will be characterized to determine which are best for supporting growth of normal human mammary epithelial cells in culture.

Project Officer: Chester V. Piczak, B.S.
Program: Breast Cancer Experimental Biology
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Therapy of Patients with Stage II Carcinoma of the Breast

Principal Investigator: Dr. Armando Guiliano
Performing Organization: University of California
City and State: Los Angeles, CA

Contract Number: NO1-CB-43917
Starting Date: 6/17/74 Expiration Date: 6/16/81

Goal: To evaluate in patients with Stage II carcinoma of the breast the effectiveness of postoperative adjuvant chemotherapy and two forms of adjuvant chemoimmunotherapy.

Approach: Patients with positive axillary lymph nodes were randomly assigned to one of the following treatment schedules: (1) cyclophosphamide, methotrexate, and 5-fluorouracil (CMF); (2) CMF plus BCG; or (3) CMF plus BCG plus tumor cell vaccine (TCV). The tumor cell vaccine consisted of irradiated allogeneic breast carcinoma cells grown in tissue culture. Chemotherapy is administered in 12 cycles for 64 weeks. Immunotherapy was given concurrently and for one year following chemotherapy. BCG is administered by Tine technique; tumor cell vaccine was administered intradermally. Treatment failure consists of either metastases or development of carcinoma in the contralateral breast. The patients are evaluated before treatment and at intervals throughout the study.

Progress: One hundred thirty-one patients have been entered into the protocol since June 1974. The longest follow-up is 79 months. The recurrence rate for the CMF group is 6/37 (16.2%) at a 43-month mean follow-up. This group is being carefully studied to determine if prognostic factors are the same as in the CMF-BCG and CMF-BCG-TCV group. The recurrence rate for the CMF + BCG group is 23/53 (43%) and for the CMF + BCG + TCV group, 14/41 (34%) at a 59-month mean follow-up. These figures are all significantly better than the recurrence rate for untreated historical controls. There is no significant difference for recurrence and survival between the pre- and postmenopausal groups.

Project Officer: Mary E. Sears, M.D.
Program: Breast Cancer Treatment
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Epidemiology of Benign Breast Disease

Principal Investigator:	Dr. Gary H. Spivey
Performing Organization:	University of California
City and State:	Los Angeles, CA

Contract Number: NO1-CB-74202
Starting Date: 8/15/77 Expiration Date: 8/14/82

Goal: To examine the epidemiology of major types of benign breast disease and to compare identifiable risk factors for benign diseases with known risk factors for breast cancer. To examine a histologic classification scheme based on grading of cellular atypia in comparison to the conventional histologic classification.

Approach: Women with first biopsies for benign breast disease in participating hospitals are identified from pathology records and admitted to the study. They are selected to maximize representation of various histologic subtypes. Biopsy slides of participants are reviewed by two pathologists and classified according to two classification systems. A subcategory of women with breast cancer is included. Two types of controls are used, a hospital control and a friend control. Information on epidemiologic characteristics is obtained by a questionnaire covering a wide range of topics including environmental influences; familial cancer patterns; medical, maturation, and reproductive history; and other endocrine-related subjects. Epidemiologic characteristics of different histologic types of benign breast disease will be compared to each other and to those of breast cancer.

Progress: Identification, recruitment, and interview of study subjects are almost complete. To date, 2,190 subjects have been interviewed, 121 have been assigned to interview, and 76 are still being recruited. We are currently coding, keypunching, and cleaning the remaining data and beginning preliminary analyses on a subset of the study population. At this time we have 1,879 questionnaires on-line and cleaned.

Project Officers: Elizabeth P. Anderson, Ph.D., B. J. Stone, Ph.D.
Program: Breast Cancer Epidemiology
FY 81 Funds: $22,500

CONTRACT RESEARCH SUMMARY

Title: Prediction of Hormone Dependency in Human Breast Cancer

Principal Investigator: Dr. Elwood V. Jensen
Performing Organization: University of Chicago
City and State: Chicago, IL

Contract Number: NO1-CB-43969
Starting Date: 6/16/66 Expiration Date: 6/15/82

Goal: To develop and improve techniques that will increase the predictability of response of human breast cancers to endocrine therapy.

Approach: Since 1966, Dr. Jensen has been studying estrogen receptors (ER) in human breast cancer tissues and the relationship between ER content and response to endocrine manipulative treatments. Now that the predictive value of ER measurements has been established, attention is being directed toward development of simple, inexpensive assay procedures for ER in breast cancers and evaluation of the ability of an ER assay on the primary tumor, carried out at the time of mastectomy, to predict subsequent response to endocrine therapy.

Progress: Fusion of mouse myeloma cells with splenic lymphocytes from a Lewis rat, immunized with purified estrogen receptor from MCF-7 cancer cell cytosol, yielded hybridomas secreting antibodies to human estrophilin. After cloning by limiting dilution, three hybridoma cell lines were isolated, each secreting a monoclonal antiestrophilin antibody that recognizes a different antigenic determinant on the receptor molecule. A combination of two of these antibody preparations, one used to adsorb the receptor on polystyrene beads and the second labeled with ^{125}I to measure the amount of receptor thus bound, provides an effective sandwich system for the radioimmunometric assay (IRMA) of estrophilin in breast cancers. In a preliminary evaluation with ten human breast cancer cytosols, the same relative receptor contents were found with the IRMA procedure as by sedimentation in sucrose gradients, although the absolute values obtained by the immunochemical technique were somewhat higher. The controlled pore glass bead procedure also has been compared with sucrose gradient analysis for more than 300 human breast cancer cytosols; again the same relative receptor contents were observed with the CPG method giving the same or, in some cases, higher absolute values. Clinical data abstraction for the breast cancer patients whose tumors were analyzed at the University of Chicago from 1966 to 1976 is in its final stages, and our systematic correlation of multiple parameters to provide maximum information will soon be feasible. Meanwhile, summaries of clinical abstracts are being furnished to the National Cancer Institute at the rate of about ten each month.

Project Officers: Mary E. Sears, M.D., Ihor J. Masnyk, Ph.D.
Program: Breast Cancer Treatment
FY 81 Funds: $25,000

CONTRACT RESEARCH SUMMARY

Title: Detection of Immune Complexes in Sera of Patients with Breast Cancer

Principal Investigator: Dr. M. Edward Medof
Performing Organization: University of Chicago
City and State: Chicago, IL

Contract Number: NO1-CB-84224
Starting Date: 9/1/78 Expiration Date: 8/30/81

Goal: To assay sera from patients with breast cancer, benign breast disease, and normal volunteers for immune complexes (ICs) employing multiple techniques for IC quantitation, then to correlate levels where applicable with presence or absence of tumor (or benign disease), tumor progression, response to therapeutic intervention and clinical course; to determine how hormonal status, past history and other clinical factors influence results, and to establish the relationship between IC data and pathologic features and other laboratory parameters.

Approach: Four detection techniques for ICs (Raji cell assay, conglutinin-binding assay, solid phase C1q assay, and C1q-PEG precipitation assay) are established in this laboratory and will be run on sera from new patients with breast cancer (20-30) and benign breast disease (40-50). Serial samples from patients receiving and not receiving chemotherapy and/or Tamoxifen following mastectomy will be studied. Efforts will be made to obtain sera from other investigators in the breast cancer study group, assay these sera, and correlate IC data with other markers. Serum samples will be assayed for soluble and insoluble, complement bearing and IgG-Fc accessible ICs. Data will be correlated with type of mastectomy, stage of patients, histologic type of tumor, including estrogen receptor positivity, histology of regional lymph nodes, as well as presence or absence of CEA and K-casein, ß-human chorionic gonadotropin (ß-HCG) and prolactin in selected cases.

Progress: Systems are operational for collection, coding, and storage of blood samples; assembling pertinent clinical data; and for data analysis. IC assays have been perfected and standardized. Measurements have been made on sera from more than 400 patients. Epidemiological analyses of the various patient populations have been made, including: analysis according to age, race, age at menarche and menopause, where applicable, pregnancy data and risk factors. Risk factors include family history of cancers, duration of nursing, years of birth control pills, use of postmenopausal estrogens and exposure to smoking and carcinogens. Correlative analyses between IC levels and clinical data and other laboratory parameters have been made. Analyses so far indicate that 1) the Raji assay is most effective in differentiating cancer and noncancer groups, 2) ICs are present in certain types of benign disease, 3) there may be a correlation with estrogen receptor content, and 4) IC levels are affected by certain types of past history.

Project Officers: D. Jane Taylor, Ph.D., Donald E. Henson, M.D.
Program: Breast Cancer Diagnosis
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Role of Dietary Factors and Non-contraceptive Estrogens in Breast Cancer

Principal Investigator:	Dr. Abraham M. Y. Nomura
Performing Organization:	Cancer Center of Hawaii University of Hawaii
City and State:	Honolulu, HI

Contract Number: NO1-CB-53884
Starting Date: 6/30/75 Expiration Date: 6/29/81

Goal: To determine in postmenopausal women if there is an association of breast cancer with specific dietary factors and/or the use of menopausal estrogens.

Approach: A case-control approach is being utilized with a personal interview to collect information on past history of drug usage (including menopausal estrogens) and usual weekly dietary intake. Breast cancer cases from three selected populations (ages 45-74) are identified: (1) the Caucasians in Hawaii, who are at high risk for breast cancer; (2) the Japanese in Hawaii, who are at intermediate risk; and (3) the Japanese in Fukuoka, Japan, representing a low-risk population. For each case, a neighborhood and hospital control, matched by race and age, is interviewed. Attempts are made to verify the drug history with the subject's personal physicians, and a subsample of the study population receives a repeated dietary interview to assess its reliability.

Progress: The study originally aimed to interview 200 cases and 400 controls in each of the three ethnic groups. The Fukuoka portion of the study has been completed with the recruitment of 213 cases, and their respective hospital and neighborhood controls. The percentages of refusals were 1%, 4%, and 13% for cases, hospital controls, and neighborhood controls, respectively. In Hawaii, interviews have been completed on 187 cases, 180 hospital controls, and 177 neighborhood controls among the Japanese and 163 cases, 159 hospital controls, and 141 neighborhood controls among the Caucasians, as of October 31, 1980. The current percentages of refusals are as follows: 15%, 18%, and 14% for the Japanese and 18%, 28%, and 15% for the Caucasian cases, hospital controls, and neighborhood controls, respectively.

Project Officers: Elizabeth P. Anderson, Ph.D., David Levin, M.D.
Program: Breast Cancer Epidemiology
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Effect of Chemotherapy-induced Endocrine Alterations on Stage II Breast Cancer

Principal Investigator: Dr. Tapas K. DasGupta
Performing Organization: University of Illinois
City and State: Chicago, IL

Contract Number: NO1-CB-84221
Starting Date: 7/1/78 Expiration Date: 6/30/81

Goal: To determine if the prolongation of the clinically disease-free interval produced by adjuvant chemotherapy is a result (1) of direct anti-cancer actions, (2) indirect action via endocrine organ changes, and (3) combination of 1 and 2.

Approach: In the clinical study, premenopausal women with operable stage II breast cancer are registered to obtain preoperative hormone profiles. If 1 or more axillary nodes contain histologically proven metastases, the patient enters the adjuvant chemotherapy program. Estrogen (ER) and progesterone (PGR) receptor assays are performed. Study patients receive 12 courses of cyclophosphamide (cytoxan), methotrexate, and 5-fluorouracil (5-FU). Blood samples are drawn during the first 2 weeks of each 28 day cycle of chemotherapy for 12 consecutive cycles during CMF administration and every 3 months thereafter to determine hormone levels. In animal studies 1-methyl-1-nitrosourea (NMU) is used to induce mammary tumors in BUF/N rats. The effects of CMF on tumor dynamics and hormone levels will be determined.

Progress: To date 3 of 34 (9%) evaluable patients receiving CMF chemotherapy have failed. None have completed treatment. All were ER^-. Table 1 shows the incidence of ER and PGR in stage II patients. Of 34 tumor cytosols 26 (76%) have been assayed for PGR. Nineteen of 34 tumor cytosols (56%) were ER^+ (>3 fm/mg protein).

Table 1. Receptor Distribution in Stage II Breast Cancer Cytosols

ER^+PGR^+	ER^+PGR^-	ER^-PGR^+	ER^-PGR^-	ER^+PGR^{NA}	ER^-PGR^{NA}
7/26 (27%)	8/26 (31%)	0/26	11/26 (42%)	4/8 (50%)	4/8 (50%)

NA: Not assayed

Tumor and cytosol ER incidence and tumor latency in BUF/N rats are dependent on the day of the estrous cycle NMU is administered. Ovariectomy produced a complete response (25%) and partial response (47%) within 2 weeks. As a single agent, only cytoxan produces a significant alteration in estrous cyclicity and reduction in tumor growth taken as a percentage of pretreatment volumes. Cytoxan does not significantly affect tumor growth in ovariectomized rats. The effect of cytoxan, methotrexate and 5-FU as single agents and in combination on tumor growth and hormone levels in intact and ovariectomized animals is currently being evaluated.

Project Officer: Mary E. Sears, M.D.
Program: Breast Cancer Treatment
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Benign and Non-invasive Breast Lesions in Groups at Different Risk for Breast Cancer

Principal Investigator: Dr. Sue Amelia Bartow
Performing Organization: University of New Mexico
City and State: Albuquerque, NM

Contract Number: NO1-CB-84231
Starting Date: 9/30/78 Expiration Date: 9/29/82

Goal: To investigate whether population groups with low incidence of breast cancer also have a low prevalence at autopsy of benign breast lesions.

Approach: Combining the resources of the population-based New Mexico Tumor Registry, the State's Medical Investigator's Office and the Medical School Departments of Pathology and Radiology, we propose to examine and compare benign breast lesions in three ethnic groups in an autopsy series--Anglos, Spanish Americans, and American Indians. These three groups are all at differing risk for breast cancer. The incidence rates and histopathologic distributions of breast cancers are already known from Tumor Registry data. The autopsy series to be examined will include about 500 women in three years, 230 Anglo, 140 Spanish American, and 130 American Indian. Breast lesions will be classified pathologically. Radiological studies of the specimens by both clinical mammography and high resolution techniques will be compared with histopathological findings. Medical, reproductive, and related history of each case will be obtained from the family physician or medical records if at all possible.

Progress: A total of 212 cases have been accessioned into the study (127 Anglo, 52 Spanish, and 33 American Indian). Autopsies are now being preferentially performed on the low risk Spanish and Indian women. Medical histories on 182 cases include 80 complete interviews, 5 incomplete, 39 pending, and 58 unable to complete. Radiologic analysis of 178 cases indicates the following: prevalence of "high risk" patterns by Wolfe's classification is greater in the Anglo than in the Indian population; high risk patterns are more often present in the >40 age group in Anglo women than in Spanish/Indian women. Morphologic analysis of 100 cases showed the following trends: earlier and more complete involution of the non-fat breast tissue in Indian and Spanish women as compared to Anglo women; presence of cystic change and ductal epithelial proliferative changes in all three ethnic groups, increasing with age. Correlation of morphologic findings with breast parenchymal patterns of Wolfe's mammographic classification groups shows the patterns to be the result of varying degrees of periductal and intralobular fibrosis. Presence of ductal epithelial proliferative changes does not appear to correlate significantly with the "higher risk" mammographic breast patterns. Computerization of the data, now under way, will be necessary to analyze more completely the data being collected.

Project Officers: Elizabeth P. Anderson, Ph.D., Louise Brinton, Ph.D.
Program: Breast Cancer Epidemiology
FY 81 Funds: $30,000

CONTRACT RESEARCH SUMMARY

Title: Methods to Predict Chemotherapy Sensitivity

Principal Investigator: Dr. Russell Hilf
Performing Organization: University of Rochester
City and State: Rochester, NY

Contract Number: NO1-CB-74204
Starting Date: 7/15/77 Expiration Date: 7/14/82

Goal: To develop a reliable prognostic test that will predict the efficacy of chemotherapeutic agents in the treatment of individual breast cancer patients.

Approach: This project will perform a battery of selected enzymes in primary and metastatic breast cancer specimens and will develop mathematical models based on the biochemical profile. The enzymes include lactate dehydrogenase, pyruvate kinase, glucosephosphate isomerase, isocitrate dehydrogenase, phosphoglucomutase and glucose 6-phosphate dehydrogenase; DNA and protein levels will be measured. Hormone receptor assays and histopathology will also be performed. Data concerning the patients' biological and oncological histories will be acquired, evaluated and stored. Analyses of the combined data will test the predictive accuracy of the mathematical model constructed from the biochemical profile.

Progress: Accession of cases for the project continues at the anticipated rate as follow-up data on response or recurrence are obtained and entered into the computer file from the forms devised for this study. More than 350 cases have been identified as eligible according to the criteria established at the outset. A logistic regression model has been developed, based on the activities of LDH and the product of the activities of PK x GPI x ICD. We have 93 patients with advanced disease, classified according to a 50% probability estimate as the cut-off for response vs. no response. For non-responders, the model correctly classified 58/61 (95%) and for responders 22/32 (69%), an overall accuracy of 80/93 (86%). We have identified 82 patients receiving adjuvant therapy; 54 have had recurrences. Patients recurring have demonstrated low enzyme activity profiles. We have now applied a statistical method of Cox in which biochemical parameters act as regressor variables in the hazard function and are related to time to recurrence. Employing maximum log-likelihood criteria for model selection, we have developed models that gave a negative coefficient for GPI indicating that higher GPI activity suggests decreasing hazard, i.e., recurrence. Additional factors were found to be menopausal status. A further extension to patients receiving no therapy (about 160 cases) is under way and here we are finding that enzymes and DNA may have prognostic implications. In each of these clinical groups, ER status does not appear to offer prognostic value for disease outcome in patients receiving cytotoxic chemotherapy.

Project Officer: Mary E. Sears, M.D.
Program: Breast Cancer Treatment
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Biochemical Mechanism of Endocrine-induced Breast Cancer Regression

Principal Investigator: Dr. William L. McGuire
Performing Organization: University of Texas Health Science Center
City and State: San Antonio, TX

Contract Number: NO1-CB-23862
Starting Date: 6/1/72 Expiration Date: 5/31/82

Goal: To obtain new information of the hormonal control of breast tumor growth and to identify those breast cancer patients whose disease will respond to hormonal manipulation.

Approach: To provide correlations of estrogen and progesterone receptor measurements with prognosis at the time of mastectomy and response to endocrine therapies. To evaluate histochemical methods of measuring steroid receptors.

Progress: Clinical correlations of steroid receptor in primary breast cancer and prognosis. -- We have completed our double blind study with Dr. Ed Fisher in Pittsburgh correlating ER content and histopathologic variables. We find several histologic variables that correlate with estrogen receptor status. Highly statistically significant correlations between ER content and histologic grade and nuclear grade, tumor necrosis, elastosis and lymphoid cell infiltration were observed. We conclude that ER is a biochemical marker for the degree of differentiation of human breast cancer providing in part a rationale for the observed differences in biologic behavior between receptor positive and negative tumors.

We are concentrating our efforts in obtaining clinical follow-up data in patients in whom we have assayed ER and PgR. The coming year will be devoted to increasing the follow-up and analyzing the data.

Clinical Follow-up of Breast Cancer Data

	San Antonio	Downstate	Cleveland	New Orleans	Total
All cases assayed for receptor	1718	676	1357	311	4062
# cases with clinical follow-up	1095	201	1037	178	2511
					62%

Immunocytochemistry -- We have tested probes that might detect ER using cytochemical techniques. So far none is successful and we have found many that other people use are useless. Recently we have obtained some new steroid conjugates that might avoid some of the current difficulties and are currently testing them.

Project Officer: Mary E. Sears, M.D.
Program: Breast Cancer Treatment
FY 81 Funds: $112,600

CONTRACT RESEARCH SUMMARY

Title: Risk Associated with In Situ Carcinoma and "Precancerous" Mammary Hyperplasias

Principal Investigator: Dr. David L. Page
Performing Organization: Vanderbilt University School of Medicine
City and State: Nashville, TN

Contract Number: NO1-CB-74098
Starting Date: 7/15/77 Expiration Date: 4/14/81

Goal: To compare subgroups of females regarding their incidence of breast carcinoma during a 10 to 25 year interval after biopsy diagnosis of in situ carcinoma and mammary epithelial hyperplasias.

Approach: This will be a retrospective cohort study in which slides have been reviewed and classified on over 11,000 breast biopsies performed during 1952-1968. The study population with proliferative disease will then be contacted and follow-up information on each subject obtained regarding subsequent development of mammary carcinoma, as well as other pertinent clinical and epidemiological data. The control group will be composed of patients with biopsy but no evidence of proliferative lesions. An effort will be made to identify those specific breast lesions or combinations of lesions which are associated with an increased risk of development of breast cancer. Non-anatomic risk factors will also be correlated.

Progress: There have been 3,519 contact letters mailed with 2,807 completed questionnaires on file. Operating surgeons and their office personnel have given invaluable aid in these efforts. A data quality assurance program has been designed and implemented. Two programs for statistical analysis have been written and are in place for final analysis. Histologic classification is complete for all biopsies in the study. The total number of biopsies with hyperplastic lesions or carcinoma in situ is 2,735. One hundred sixty-six biopsies are identified with carcinoma in situ. One hundred sixty biopsies with atypical lobular hyperplasia and 690 biopsies with severe hyperplasia of ductal type are identified. There are 1,418 biopsies demonstrating ductal hyperplasia of moderate degree.

We have completed review and follow-up of 28 patients with ductal carcinoma in situ treated by diagnostic biopsy only. Three of these patients were followed less than three years, dying of causes unrelated to breast disease or treated by bilateral mastectomy. Of the remaining 25 patients treated with biopsy only, 28% developed invasive breast carcinoma with an average follow-up of 16 years. All invasive breast carcinomas appeared in the same breast demonstrating in situ carcinoma in the biopsy. Six of these were in the same quadrant and one was in an adjacent quadrant. The average interval to invasive carcinoma development was 6.1 years (range 3 to 11 years). The average age at biopsy for all women was 52. Four of the seven women developing invasive carcinoma have developed distant metastases, with three of them dying of metastatic breast cancer.

Project Officer: D. Jane Taylor, Ph.D.
Program: Breast Cancer Diagnosis
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Biologic Markers in Breast Cancer: Patient Resource

Principal Investigator: Dr. Leslie W. Whitney
Performing Organization: Wilmington Medical Center
City and State: Wilmington, DE

Contract Number: NO1-CB-74137
Starting Date: 9/1/77 Expiration Date: 8/31/81

Goal: To develop a Breast Cancer Task Force specimen resource for blood from breast cancer patients and controls to be used in a search for and verification of new breast cancer markers.

Approach: Thirty milliliters of blood were collected from all project participants with malignant breast lesions and all benign patients who developed malignant breast lesions during the first year follow-up. These specimens are processed, shipped, and stored at -70°C at an NCI-designated blood bank facility with appropriate clinical data.

Progress: In the first contract year (9/1/77 - 8/31/78) 65 patients were entered into the study, 27 of whom have malignant disease. From these 27 malignant patients we have completed a 3-year follow-up on 21. Of the remaining 6, 2 have expired, 1 has moved out of state, 1 refused, and 2 are unable to have blood drawn at the present time. In the second contract year (9/1/78 - 8/31/79), 248 patients were entered, 80 of whom have malignant disease. We have obtained a 2-year follow-up on 67 malignant patients; of the remaining 13, 5 have refused 6 have expired and we are unable to contact the remaining 2.

For the 206 benign patients in the studdy, a follow-up questionnaire with cover letter was sent to all. A 1-year follow-up was completed on 198 patients either by direct mail return, telephone contact with the patient if no mail return, or contact with doctor's office or hospital clinic if we were unable to contact the patient. One patient refused follow-up and 7 had no doctor contact and have moved leaving no forwarding address.

From 575 patients, 5,917 vials of serum have been shipped to the storage facility at Mayo Clinic.

Project Officers: Ihor J. Masnyk, Ph.D., Mary E. Sears, M.D.
Program: Breast Cancer Treatment
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Produce and Identify Antibodies to Collagens/Procollagens and/or Related Enzymes

Principal Investigator: Dr. Heinz Furthmayr
Performing Organization: Yale University
City and State: New Haven, CT

Contract Number: NO1-CB-84225
Starting Date: 9/18/78 Expiration Date: 9/17/81

Goal: To prepare immunochemically defined antibody reagents to collagen of types I, II, III, IV (basement membrane), AB (fetal collagen), procollagens of types I and III and mouse collagen of types I, III and IV.

Approach: Studies include: (1) Isolation and purification of collagens from calf, human, and mouse tissue for immunization, affinity columns, and serological testing; 2) immunization of rabbits and mice; 3) serological screening of antisera during immunization and after final bleeding; 4) obtaining monoclonal antibodies to type IV collagen and type I and III procollagen by the somatic cell hybridization technique; (5) isolation and purification of antibodies specific for each collagen; and (6) characterization of the isolated antibodies.

Progress: In addition to progress reported in the previous two years, small amounts of the aminoterminal propeptide of type I and type III collagen were obtained to be used for producing monoclonal antibodies. Type IV collagen (pepsin extract) from calf lung and human placenta and a fragment (E-chain) presumably derived from basement membrane collagen were isolated. The preparations, in addition to biochemical characterization, were analyzed by the new technique of rotary shadowing, which has been introduced in the laboratory recently. Groups of 10 rabbits each were immunized with mouse collagen type I and type III and pure antibodies were isolated to mouse type I thus far. Currently, work is progressing on the isolation of mouse type III antibodies. Antibodies were produced and isolated to the "E-chain," which react with basement membranes in immunofluorescence experiments. During the past eight months they have been working on the application of the monoclonal antibody technique and have obtained 9 clones of cells which synthesize IgM antibodies to calf type IV (lung) collagen and four of these monoclonal antibodies react by tissue fluorescence. These antibodies at present do not appear to cross-react with human basement membranes as shown by serological or by immunofluorescence tests. Characterization of monoclonal antibodies to type IV collagen from human lung is being done. Hybrid cells were produced which synthesize antibodies to human type V (AB_2) collagen. These hybrid cells have not yet been cloned, however. Mice were immunized with propeptide type I and the first fusion experiment is planned in the near future.

Project Officer: Chester V. Piczak, B.S.
Program: Breast Cancer Experimental Biology
FY 81 Funds: 0

DESCRIPTION

The Cancer Diagnosis Research Program emphasizes research in early detection, diagnosis (which includes staging and prognosis), tumor localization, and monitoring the changes during therapy or progression of disease. The program also seeks to apply the knowledge obtained to appropriate populations for clinical evaluaation. Projects in these areas are frequently concerned with improvement of existing techniques as well as the development of new tests and procedures. Many of the projects in the Cancer Diagnosis Research Program have begun in a more basic area such as, Tumor Biology, Tumor Immunology, or General Medical Sciences for instrument development. As a basic concept becomes potentially useful in one of the areas of cancer diagnosis the project may be transferred to the Cancer Diagnosis Research Program. In the earliest stages, diagnostic research is not necessarily site (or even disease) oriented.

The major objective of the Program is to recognize or detect cancer at the earliest possible stage to allow appropriate therapy to begin. Early detection and early treatment should improve the chances for the control of cancer, decrease mortality from the disease and increase survival and quality of life of those with cancer. Additionally, early detection is providing greater understanding of the natural history of different types of cancer in the early stages of disease.

Since the techniques of cancer detection and diagnosis are useful for many, or all, types of cancer the divisions of the program are not by cancer type or organ site, but by technical discipline. The Diagnosis Research Program consists of projects in eight disciplinary categories: Biochemistry, Immunodiagnosis, Cytology, Pathology, Radiological Imaging, Non-Radiological Imaging (Ultasound, Nuclear Magnetic Resonance, Thermography and Microwave), Nuclear Medicine and those projects that are clearly Multiple Disciplinary.

The distribution of contracts and grants currently included (FY1980) in the Diagnosis Research Program into the various categories in summarized in the following table. Each category is discussed in the sections following the table.

TABLE 1

CANCER DIAGNOSIS RESEARCH PROGRAM

ALL PROJECTS EFFECTIVE DURING FISCAL YEAR 1981

Number	Category	Grants		Contracts	
		Number	Current Funding (in Thousands)	Number	Current Funding (in Thousands)
1	Biochemistry	24	1,503	1	0
2	Immunodiagnosis	25	2,522	21	443
3	Cytology	23	2,066	7	553
4	Pathology	4	266	0	0
5	Radiological Imaging	16	759	4	383
6	Non-Radiological	12	1,198	3	262
7	Nuclear Medicine	15	1,437	0	0
8	Multiple Disciplines	1	71	8	3,122
	TOTALS	120	9,822	43	4,763

1. BIOCHEMISTRY

Biochemical methods to improve diagnosis and detection of cancer involve the study of a variety of substances such as hormones, enzymes, proteins and metabolic products in the circulation and in other biological fluids, as well as the study of surface characteristics of tumor cells and chemical characterization of tumor cells.

Under hormonal studies, the measurement and mode of action of the multiple forms of human growth hormone are being studied under grant CA-14025. The objective of grant CA-23848 is to develop a simple and rapid method of detecting estrogen receptors in the endometrium and mammary gland using fluorescein-labeled hormones and fluorescence microscopy. The results are being correlated with the clinical response of the patients to endocrine therapy. Identification, isolation and characterization of thyroid hyperfunction in patients with trophoblastic tumors, especially hydatidiform mole, are being pursued under grant CA-31218. A series of experiments have been proposed in grant CA-29062 to evaluate the clinical use of a material which is cross-reactive to vasoactive intestinal peptide (VIP) as a biochemical marker to refine the diagnosis of acute leukemias.

A variety of enzymes are being studied for their correlation with different cancers. Histaminase and an isozyme of alkaline phosphatase (FHAP) are being investigated as general cancer markers in grant CA-26652 and contract CB-74173, respectively. The biochemistry of isozyme 5 of acid phosphatase and its clinical implications in the diagnosis and prognosis of prostatic cancer and of hairy-cell leukemia will become topics of investigation for a new grant CA-31187. Studies of 5'-nucleotide phosphodiesterase which has been shown to be elevated in patients with known hepatic metastases from mammary carcinoma will be continued under grant CA-25376. A basis for characterizing and classifying human lung tumors and revealing essential biochemical pathways vulnerable to chemotherapy by means of quantitative enzyme profiles is being sought under grant CA-25016. Enzymes are being determined in plasma, blood cells and liver biopsy samples in grant CA-22065 to ascertain their predictive value in diagnosis and in monitoring of lymphoma patients during therapy. Serum, urine and CSF ribonucleases in tissues and body fluids of healthy subjects and breast cancer patients will be isolated, characterized and correlated with disease status under grant CA-19606. In grant CA-25548 human tumor cell lines will be characterized by isozyme phenotyping to confirm whether they are bona fide representatives of the tumors from which they were derived. Differentiation of lymphocytes by the enzyme marker, terminal deoxynucleotidyl transferase, (TdT) is being investigated under grant CA-22599 by determination of the relationship of presence or absence of the enzyme to particular cell sets and to tumors representing those cell sets.

Proteins as discriminants of cancer are being investigated under several grants. Protein analysis of pancreatic secretions is being probed for diagnostic potential in pancreatitis and pancreatic cancer under grant CA-14380. Most of the research effort in grant CA-19634 is devoted to a characterization of lipoprotein differences, qualitative and quantitative, between mammary carcinoma patients, normal individuals with a family history of cancer and those

with a negative family history of breast cancer. Intercellular matrix proteins are being extracted from human chondrosarcomas in grant CA-23945 and compared with normal articular cartilage to evaluate degree of malignancy and possibly grade chondrosarcomas biochemically as well as morphologically. A new investigator research grant CA-30667, recently awarded, aims to exploit the differences in lectin binding characteristic of the mucin found in normal colon and abnormal colon, malignant and premalignant, to predict the risk of developing colon cancer.

Urinary nucleoside breakdown products of tRNA are being measured in cancer patients in grant CA-25210 to explore the molecular mechanism responsible for increased excretion in cancer patients. In grant CA-14185 modified nucleosides derived from the turnover of human RNA and from the nucleic acid anabolic processes and present in urines of cancer patients will be evaluated as possible quantitative tumor markers. The values of guanosine monophosphate (cyclic GMP), and adenosine monophosphate (cyclic AMP) in plasma and urine of patients with precursor lesions and gynecologic neoplasms are being determined in grant CA-25357 to ascertain their usefulness in screening, detection, diagnosis, treatment and follow-up of patients with gynecologic neoplasms.

A "myasthenic" substance found in small cell lung cancer tissue is being studied as a possible aid in detection of lung cancer under grant CA-22885. The aim of CA-21958 is to compare quantitatively and qualitatively the serum heteroglycan fractions of tumor bearing animals with those from controls to ascertain whether these can be utilized for detection of malignancies and for monitoring of tumor burden. Electron paramagnetic resonance (EPR) measurements of cupric ion bound to ceruloplasmin are being made to ascertain whether these can indicate the presence of cancer in humans under grant CA-14335 and to correlate changes with success or failure of treatment. Gas chromatography of the colonic microbial metabolites in breath will be performed in grant CA-29056 to test the hypothesis that these metabolities may be useful markers for increased risk of developing colonic cancer.

2. IMMUNODIAGNOSIS

The portion of the Diagnosis Program classified as Immunodiagnosis can be subdivided into projects dealing with circulating tumor antigens or markers, such as oncofetal antigens, hormones, enzymes, and glycoproteins; projects dealing with tumor associated antigens, research in localization of tumors by radioimmunodetection; studies of lymphocytes in host-tumor relationships, and projects dealing with antibodies to tumors (including immune complexes).

The carcinoembryonic antigen is the most widely utilized circulating oncofetal tumor marker and contract CB-33848 deals with the prognostic and monitoring value of CEA following therapy of colorectal and lung cancer. Additionally there is a study on the heterogeneity of CEA, grant CA-24376, and comparison of new gastrointestinal cancer antigens with CEA and improvement of their clinical use in program project grant CA-04486.

Several projects are investigating the relationship between hormone levels and cancer: calcitonin and β-lipotropin are subjects for two grants, CA-22137 and CA-23382, respectively. Two other studies of serum calcitonin as a screen for family members of patients with medullary thyroid cancer are supported by

grant CA-22595 and contract CB-63994. The role of serum thyroglobulin levels as markers of tumor recurrence in thyroid cancer is being investigated under grant CA-25338.

Two studies of enzymes as markers for cancer deal with measurement of serum levels of tyrosinase in patients with melanoma, grant CA-25381 and of UDP-galactosyltransferase in patients with ovarian and breast carcinoma in contract CB-84260. The prostate is the organ site involved in contract CB-74169 evaluating acid phosphatase in a screening population and in grant CA-23990 testing acid phosphatase and ribonuclease as markers for the early detection of prostatic carcinoma. The objective of a new grant, CA-29225, is to develop an immunohistochemical technique for the visualization of a monocyte esterase marker to be employed in the differential diagnosis of subtypes of leukemias.

Proteins or their degradation products have been detected in body fluids and have demonstrated correlation with the presence of cancer. The role of SAA, a major protein constituent of secondary amyloid is being investigated as a marker of tumor recurrence, response to therapy and immune function in cancers of the lung and gastrointestinal tract on grant CA-22141. Gp 48, a major group of glycoproteins sythesized and released into organ culture from breast adenocarcinoma specimen are being assessed for their diagnostic significance in grant CA-24645. A glycoprotein, EDC1, is being monitored in both urine and plasma of breast cancer patients and controls for its immunodiagnostic value under contract CB-84308. Studies are being continued under grant CA-31762 to biochemically characterize a glycoprotein surface antigen found on myeloblasts of leukemia patients, prepare antiserum to it and monitor its efficacy in predicting relapse of leukemia patients in remission.

Tumor associated antigens studies are under way for many organ sites: breast, CA-20286; cervix and head and neck, CA-84267; urogenital tract, CA-27213; melanoma, CA-30019; mesothelioma, CA-27081; colon, CA-26246, CB-84259, and CB-84257. Studies of nuclear antigens associated with normal and leukemic human blood cells to determine their usefulness as markers in hematopoiesis are being supported by grant CA-26948.

Several studies are concerned with techniques for labeling antibodies with radionuclides for tumor detection and localization. Grant CA-30255 is directed towards localization of germ-cell tumors and hepatomas which produce alphafetoprotein by labeling of monoclonal antibodies with ^{131}Iodine, ^{99}Technetium and ^{111}Indium. An approach is being tested under grant CA-28462 to develop a better technique for labeling antibodies to human serum albumin (HSA) with ^{111}In or ^{99}Tc or ^{128}I, and studying the effect of various conditions, of conjugation on accelerated blood clearance and retention of immunological activity. The objective of grant CA-17742 was to study conditions favoring the localization of CEA-containing human tumors in animal systems by means of radiolabeled anti-CEA immunoglobulins and total-body photoscanning. Grant CA-25584 is a continuation of the program of CEA-tumor radioimmunodetection and involves planning a clinical trial of patients with proven malignancy to further evaluate its use in initial tumor diagnosis and in the management and clinical staging of cancer patients. A new grant CA-29639 will concern itself with the development of a method for melanoma localization using radiolabeled monoclonal antibody fragments against p97 antigen and imaging by emission tomography.

Lymphocytes and monocytes in host tumor responses are the subject of several projects. The development of clinically useful diagnostic tests based on the selective binding of bacteria and antibody-coated bacteria to lymphocyte subpopulations is being undertaken under grant CA-29552. A contract, CB-84261, has been involved in an extensive effort to evaluate lymphoid differentiation antigens, particularly those on bone marrow and thymus cells, as potential immunodiagnostic markers for leukemia and lymphomas. The relationship between the clinical status of cancer patients and the functional activity of their monocytes in vitro is being determined under contract CB-74121. Contract CB-74131 is concerned with defining optimal cryopreservation techniques of human monocytes to preserve antibody-dependent cellular cytotoxicity for immunologic studies.

Circulating antibodies to tumor antigens are being studied in patients with melanoma, in contract CB-74120; while the presence of circulating immune complexes is being quantitated and analyzed in a number of cancers including colon, breast and melanoma under contract CB-84262. Antibodies are also serially measured in mice while developing induced tumors in contract CB-74134. Investigations of the expression of the major virion glycoprotein gp52 of MMTV on late-occurring mammary tumors in mice and its potential as a tumor marker will be pursued under a new grant, CA-28305.

In addition to the research grants and contracts, there are contracts for the collection and storage of serum samples from patients with cancer and other acute and chronic diseases and during the course of therapy for certain cancers. These contracts, CB-33914, CB-04350, CB-74210, and CB-84258, have been invaluable for the rapid evaluation of a wide variety of serologic tests for cancer that come to the attention of NCI. CEA levels on blood stored at the NCI-Mayo Serum Bank are performed under contract CB-23854. A tissue culture bank for cell lines which can be utilized by an investigator for research in cancer immunodiagnosis is maintained under contract CB-43854.

3. CYTOLOGY

Diagnostic cytology research projects include the development of automated instrumentation and cell markers that can be used to differentiate normal and atypical cells. Instruments undergoing development and testing are those of high resolution slide based, grants, CA-13271, CA-28833, CA-27313, and CA-31049 and contracct CB-33873, and flow fluorometric types, contracts CB-40300 and CB-33862. Development, construction and testing of an ultrafast optcal scanner for microscopic specimens, grant CA-24466, will make possible the automated search for abnormal, transformed or cytochemically marked cells in microscopic preparations. Single cell classification algorithms employing the current state of the art in digital image processing, scene segmentation and image acquisition hardware are being developed and tested in contract CB-70314. The classification algorithm chosen with human interaction was found to perform at an acceptable error rate. A cost/utility analysis indicates that the chosen algorithms can operate with error rates adequate for routine screening.

A flow instrument currently undergoing testing uses dual staining and analysis with a dual laser beam sorter, contract CB-40300. In addition, a slit-scan using a combined static and flow system is now being tested to

determine the system characteristics including rate and causes of false alarms, contract CB-33862 and grant CA-30582. Quantitative descriptors of normal and abnormal cells include cytochemical and immunological markers which increase the potential sensitivity and specificity of sensor systems.

Two different systems are under development to place individual sorted cells on slides for subsequent retrieval and analysis, grants CA-28886 and CA-28706.

Chemical synthesis of cytochemical probes, grants CA-28770 and CA-30148, with sharp fluorescence emission spectra will enhance multiple staining of cells for flow systems and for cells on slides in static systems. Cellular fluorescent markers under investigation also include studies of fluorescent substrates for demonstration of cAMP phosphodiesterase, adenyl cyclase, and acid phosphatase, grant CA-19552; acridine orange, contract CB-33862; and chromomycin A3, contract CB-40300. Cellular DNA content and size (as measured by orthogonal light scatter) have been shown to detect abnormal cells, contract CB-40300. Cell surface antigens may also be used as markers for abnormal cells. With appropriate fluorescent tagging of these antigens, normal and abnormal cells may be differentiated by automated instruments. Potentially useful markers being studied are Herpes simplex virus related antigens, grant CA-28724 and contract CB-74170, and nucleolar antigen, grant CA-28771. In addition, cytochemical and biophysical probes of nuclear and cytoplasmic structure are being used to distinguish normal and malignant cells, grant CA-28704.

Analysis of the performance of automated systems, comparison of instrumental or system classification and manual microscopic classification utilizing standard morphologic criteria is studied under contract CB-74190. In the same contrct, programming of cell recognition algorithms continues with emphasis on scene segmentation techniques.

Flow cytometry is used in grant CA-27283 to develop an assay for detecting transformed cells (by chemical carcinogens) differentially labeled with fluorescamine. In addition, the nature and functional significance of a hyaluronidase sensitive "barrier" surrounding transformed cells is being investigated.

To better understand and treat lymphoproliferative disease, flow microfluorometry analysis of human lymphoid malignancies is under investigation, grant CA-23393, with the hope that malignant subpopulations can be identified by a two parameter analysis for size and surface immunoglobulin. In addition, it is hoped that the ploidy and cell cycle kinetic parameter of these cells will aid in the diagnosis, classification, scheduling and monitoring of treatment. A combined flow cytometric cell-sorting autoradiographic technique is being developed in grant CA-25348 to monitor acute leukemias of adults and children and to predict relapse and evaluate treatment protocol. Using fluorescence microscopy and flow microfluorimetry in grant CA-27123, merocyanine 540 is employed to study leukemia to characterize the dynamic changes in the staining pattern during the clinical course and to isolate and characterize hematopoietic progenitor cells. The selective staining of leukemic cells might be a useful adjunct to existing methods of monitoring the course of leukemia and of prognosis of relapse or remission. Merocyanine 540 is also utilized to elucidate the relationship between dye binding and the transformed state of cells in grant CA-28921. Leukemic cells are also being studied to determine their and to test chemotherapeutic agents for their ability to alter patterns of

cell differentiation in vivo, grant CA-22942. Study of human leukemic and preleukemic blood and bone marrow using the soft agar culture techniques has continued, grant CA-17353, to characterize the status and prognosis of hematoproliferative disorders. Measurements of the quality and quantity of colony formation appear to provide useful indicators of disease status and progression as well as diagnosis and predictions concerning response to therapy of acute nonlymphocytic leukemias and preleukemic states.

In an effort to predict the biological potential of gynecologic neoplastic lesions, a quantitative analysis of nuclear DNA content using Feulgen microspectrophotometry is under way, grant CA-24932. Determination of the nuclear DNA changes may reveal the correlation of the changes with regression, persistence and progression of squamous cancer of the uterine cervix. Earlier findings of carcinoma-in-situ of lung, intestine, ovary and bladder might be possible by using an immunocytologic technique being evaluated in grant CA-26863, to detect carcinoembryonic antigen on exfoliated cells. An extensive study to test the feasibility of screening for endometrial cancers in asymptomatic women by means of uterine sampling is being done under contract CB-84233.

The Eighth Conference on Analytical Cytology was partially supported by grant CA-29859.

4. PATHOLOGY

A system of classifying human pituitary adenomas based on electron microscopy and immunocytochemistry has been developed on grant CA-21905. To expand understanding of tumor behavior in the pyriform sinus and the oral cavity, whole organ sections of patients who undergo surgical excision have been studied, grant CA-22101, using microscopic appearance to determine size and extent of tumor, relation of tumor spread to the laryngeal framework and specific routes of tumor spread. Malignant lymphomas and leukemias are being studied on grant CA-26422 by a combination of methodologies along with routine morphology to determine the most valuable tests to provide earlier detection and more precise classification. Disaggregation and dispersion of solid tumors so that specific cells of interest may be isolated and concentrated for characterization is the goal of grant CA-23922. Contract CB-84257 utilizes immunohistochemical techniques to identify a variety of tumor associated antigens in tumor cells as a means for detection of metastatic disease in lymph nodes.

5. RADIOLOGICAL IMAGING

Several contracts and grants to improve x-ray imaging currently are under study. One contract, CB-74211, seeks to develop large area solid state image receptor for x-ray imaging and a large area electrophoretic display system for x-ray imaging is under development in contract CB-04341. A grant, CA-16543, is studying charge transfer electroradiography. Efforts to improve x-ray imaging and/or reduce x-ray exposure are subjects of several studies: contrast agents to improve CT scanning, grant CA-24879, and contract CB-84234; development of algorithms for x-ray dose reduction in CT scanning, contract CB-84235 and grant CA-31217; image reconstruction from incomplete projections, grant CA-23818; computer analysis of bone tumor roentgenograms, grant CA-06263; study of optical quality effects on lung tumor detection, grant CA-23816; study of diagnostic accuracy and x-ray image properties, grant CA-24625; development of a quick method of computing a single numbered dose index for CT scanning, grant CA-29171; and improved diagnostic quality of radiographic imaging for cancer

diagnosis, grant CA-24806. Improved imaging of breast tumors is the subject of several grants: CA-22803, computer evaluation of mammographic calcifications; CA-25372, new fluorescent x-ray tubes for mammography; CA-19622, low dose screening techniques for mammography; CA-19787, low dose breast electron radiography; and CA-26327, test phantoms for optimizing mammographic techniques. Other grants related to radiological imaging include CA-15882, construction of a transverse section x-ray camera; CA-23246, recognition of very small tumors in experimental animals; CA-24822, study of a 3-D tomogram viewer for cancer detection and therapy; CA-27823, development of a scanning equalization system for chest radiography; and CA-27875, post-mortem x-ray and histological comparison of the sella turcica and pituitary glands.

6. NON-RADIOLOGICAL IMAGING

Imaging studies in the Cancer Diagnosis Research Program involving methods other than x-ray and radionuclides include use of proton and heavy ion beams, nuclear magnetic resonance (NMR) ultrasound, and thermography. Grant CA-27021 supports a study of the imaging potential of proton, helium and carbon ion beams; extremely small tissue density differences are detected by ion beams but their lateral resolution is inferior to that of x-ray. Evaluation of a high magnetic field strength clinical NMR imaging spectrometer is being started under a new program project, grant CA-28881. Grant CA-15300 is developing NMR zeugmatographic imaging for cancer detection. Imaging with thermography at microwave and millimeter wave-lengths is being studied on grants CA-17642 and CA-28873. Several grants are investigating means to improve breast imaging with ultrasound: CA-19019, ultrasound mammography; CA-24085, quantitative ultrasound imaging of the breast; CA-24257, breast tumor diagnosis by computed ultrasound; CA-25323, ultrasonic computed tomography of breast cancer; and CA-25634, development of an ultrasonic breast tissue phantom. Contrast agents for ultrasound diagnosis are being developed in contracts CB-84236 and CB-14337. An ultrasonic probe suitable for use in endoscopes is the goal of contract CB-74136. A scanning acoustic microprobe for cancer diagnosis by external imaging is under development and testing on grant CA-25938. Transpelvic ultrasonic evaluation of the prostate to improve early detection of prostate cancer is being studied on grant CA-27895.

7. NUCLEAR MEDICINE

Several grants are devoted to production of a variety of tagged tumor-seeking agents: CA-08349, CA-15787, CA-16861, CA-18153, CA-19898, CA-24344, CA-26371, CA-26968, CA-28343, and CA-28561. Grant CA-27252 is carrying out studies of metabolism of bone scanning radiopharmaceuticals. Grant CA-24957 and CA-22578 deal with the detection of malignant melanoma with radiopharmaceuticals. Grant CA-22464 supports the study of gallium (III) and indium (III) chelates for the design of improved radiopharmaceuticals containing these metals. Program project grant CA-23417 is concerned with several basic studies to develop an improved nuclear imaging system for tumor detection. Grant CA-28105 involves development of an electronically collimated gamma tomography system for tumor imaging.

8. MULTIPLE DISCIPLINES

A number of contracts and one grant involve several disciplines and therefore are presented in this last category of multiple disciplines. Contract

CB-84232 is studying diagnostic techniques including various imaging methods to improve pancreatic cancer diagnosis. Grant CA-25582 is studying fluorescence bronchoscopy and photoradiation therapy with prophyrin derivatives. Contracts CB-74114 and CB-74212 are developing attachments for the colonoscope to facilitate its easier passage to the cecum.

A collaborative study to determine the potential of x-ray imaging and cytological examination of sputum in detection of early lung cancer is being conducted under contract CB-45007, CB-45037, and CB-53886. A fourth related contract, CB-43868, is concerned with the data management of the collaborative lung study. The longitudinal study, began in 1974, involves 30,000 men and will require several more years of follow-up before definitive results will be available.

A large-scale longitudinal colon cancer screening study using the Hemoccult test for human blood in the feces is the task of contract CB-53862. Several more years of follow-up on the 45,000 subjects will be required to define the usefulness of the screening procedure in detecting early colon cancer.

RO1-CA-14025 Multiple Forms of HGH: Measurements and Actions
Willard Vander Laan Scripps Clinic and Research Foundation

RO1-CA-14185 Modified Nucleosides in Cancer and Normal Urines
Girish Chheda Roswell Park Memorial Institute

RO1-CA-14335 EPR Studies on Detection and Treatment of Cancer
John D. Zimbrick University of Kansas Lawrence

RO1-CA-19606 Serum Urine and CSF RNases in Health and Disease
Charles A. Dekker University of California Berkeley

RO1-CA-19634 Serum Lipoproteins in Patients with Breast Cancer
Frederick Aladjem University of Southern California

RO1-CA-21958 Cancer Detection by Serum Analysis of Heteroglycans
James D. Morre Purdue University

RO1-CA-22065 Lymphoma: Diagnosis by Blood and Liver Tests
Annemarie Herzfeld New England Deaconess Hospital

RO1-CA-22599 Programs of Normal and Malignant Lymphocytes
Allen Silverstone Sloan-Kettering Institute for Cancer Research

RO1-CA-22885 Lung Cancers and Carcinomatous Neuromyopathies
Koichi Ishikawa University of Southern California

RO1-CA-23848 Steroid Uptake in Hormonally Dependent Cancers
George H. Barrows University of Louisville

RO1-CA-23945 Assessment of Malignancy in Human Chondrosarcomas
Lawrence C. Rosenberg Montefiore Hospital and Medical Center

RO1-CA-25016 Human Lung Neoplasms: Applications of Enzymes-Pathology
Olga Greengard Mount Sinai School of Medicine

RO1-CA-25210 Origins of Urinary Nucleosides in Tumor Tissue
Ernest Borek AMC Cancer Research Center and Hospital

RO1-CA-25357 Cyclic GMP Levels in Gynecologic Neoplasms
Chandralekha Duttagupta Yeshiva University

RO1-CA-25376 Development of Serum Nuclease Isozyme Test for Cancer
K. C. Tsou University of Pennsylvania

RO1-CA-25548 Isozymes of Human Tumor Cells In Vitro and In Vivo
Jorgen Fogh Sloan-Kettering Institute for Cancer Research

RO1-CA-26652 Histaminase as a Biochemical Marker for Human Cancer
Chi-Wei Lin Massachusetts General Hospital

RO1-CA-29062 Vasoactive Intestinal Peptide, Leukocytes, Leukemia
Mary O'Dorisio Ohio State University Research Foundation

RO1-CA-29056 Large Bowel Cancer and Colonic Microbial Metabolism
David Karlin University of Texas

RO1-CA-30667 A Study of Cancer Associated Colonic Mucin
Clement R. Boland Veterans Administration Medical Center

RO1-CA-31187 Biochemistry and Clinical Application of Acid Phosphatase 5
Kwok-Wai Lam Albany Medical College

RO1-CA-31218 Thyrotropins from Tumors of Trophoblastic Origin
Syed M. Amir Beth Israel Hospital

2. IMMUNODIAGNOSIS

PO1-CA-04486 Pathology of the Digestive Tract Mucous Membrane
Norman Zamcheck Boston City Hospital

RO1-CA-17742 Radiological Localization of Human Tumors
David M. Goldenberg University of Kentucky Medical Center

RO1-CA-20286 Breast Neoplasia Diagnosis with Specific Antibodies
Roberto L. Ceriani Children's Hospital Medical Center Northern California

RO1-CA-22137 Calcitonin as a Marker for Cancer of the Breast
Omega L. Silva Howard University

RO1-CA-22141 Protein SAA in Neoplastic Disease
Merrill D. Benson Indiana University School of Medicine

RO1-CA-22595 Detection of Medullary Thyroid Cancer in Families
Charles E. Jackson Henry Ford Hospital

RO1-CA-23382 Investigation of Human B-Lipotropin
Eckehart Wiedemann University of California Berkeley

R23-CA-23990 Immunodiagnosis of Prostatic Cancer
Ching-Li Lee Roswell Park Memorial Institute

RO1-CA-24376 Immunological Heterogeneity of CEA
James F. Primus University of Kentucky

RO1-CA-24645 Significance of GP48 in Diagnosis of Breast Cancer
Zoltan A. Tokes University of Southern California

RO1-CA-25338 Thyroglobulin Radioimmunoassay in Patients with Thyroid Cancer
Merl A. Charles University of California at Irvine

R01-CA-25381 Tyrosinase as a Marker for Human Malignant Melanoma
Kenji Nishioka University of Texas System Cancer Center

R01-CA-25584 Clinical CEA-Tumor Radioimmunodetection
David M. Goldenberg University of Kentucky

R01-CA-26246 Assay of Human Tumor or Organ-Associated Antigens
Calvin A. Saravis Boston City Hospital

R01-CA-26948 Nuclear Antigens as Markers in Hematopoiesis
Robert C. Briggs Vanderbilt University

R01-CA-27081 Immunodiagnosis of Mesothelioma
Gurmukh Singh University of Pittsburgh

R01-CA-27213 Detection of Urogenital Normal and Neoplastic Antigens
Robert W. Green Duke University Medical Center

R01-CA-28305 Possible Systemic Sequals for Tumor
Earl M. Ritzi University of Tennessee Center for Health Sciences

R01-CA-28462 Radiolabeling of Tumor Antibodies
William C. Eckelman George Washington University

R01-CA-29211 Immunohistologic Study of Uterine Cancer
Clive R. Taylor University of Southern California School of Medicine

R01-CA-29225 Clinical Application of Esterase, a Monocyte Marker
Kwok-Wai Lam Albany Medical College

R01-CA-29552 Differential Counting of Lymphocyte Subpopulations
Marius Teodorescu University of Illinois Medical Center

R01-CA-29639 Tumor Imaging with Radiolabeled Monoclonal Antibody
Steven M. Larson VA Medical Center

R01-CA-30019 Purification of Tumor Antigens of Defined Specificities
Risab K. Gupta UCLA Center for Health Sciences

R01-CA-30255 Immunolocalization of Human Malignant Tumors
Elliot Alpert Baylor College of Medicine

R01-CA-31762 Immunologic Diagnosis of Myeloblastic Leukemia
Robert N. Taub Columbia University School of Medicine

3. CYTOLOGY

R01-CA-13271 Automated Cancer Cell Diagnosis by the TICAS Method
George Wied University of Chicago

R01-CA-17353 Marrow Culture Studies in Human Myeloid Leukemias
Malcolm A. Moore Sloan-Kettering Institute for Cancer Research

R01-CA-19552 New Fluorescent Markers for Cancer Diagnosis
Kwan C. Tsou University of Pennsylvania

R01-CA-22942 Differentiation of Cultured Leukemic Cells
Sandra R. Wolman New York University

R01-CA-23393 Flow Analysis of Human Malignant Lymphoid Cells
Raul C. Braylan University of Florida

R01-CA-24466 Ultrafast Scanner Microscope in Laboratory Automation
Roland V. Shack University of Arizona

R01-CA-24932 Microspectrophotometric Nuclear DNA Study of Gynecologic Cancers
Yao S. Fu Case Western Reserve University

R01-CA-25348 Flow Cytometry/Autoradiography Monitoring of Leukemia
Michael Andreeff Sloan-Kettering Institute for Cancer Research

R01-CA-26863 Identification of CEA in Cytology Specimens
Robert R. Pascal St. Luke's-Roosevelt Institute for Health Sciences

R01-CA-27123 Application of Fluorescent Probes to Clinical Cancer
Jay E. Valinsky Rockefeller University

R01-CA-27283 Early Detection of Transformed Cells
Susan P. Hawkes Michigan Molecular Institute

R01-CA-27313 A Search for Preneoplastic Cell Markers in Sputum
Stanley D. Greenberg Baylor College of Medicine

R01-CA-28704 Chromatin Probes for Distinguishing Malignant Cells
Zbigniew Darzynkiewicz Sloan-Kettering Institute for Cancer Research

R01-CA-28706 Cell Positioning System: Development and Use in Cancer
Harry W. Tyrer Cancer Research Center

R01-CA-28724 Biophysical Probes for Malignant Cells
Paul Todd Pennsylvania State University

R01-CA-28770 Biophysical Probes for Automated Cytology
Kwan C. Tsou University of Pennsylvania

R01-CA-28771 Cytology Automation
Barthel Barlogie M.D. Anderson Hospital and Tumor Institute

R01-CA-28833 Cytologic Characterization of Rat Urothelium
Ian T. Young Lawrence Livermore Laboratory

R01-CA-28886 Indexed Cell Sorting
Phillip Dean Lawrence Livermore Laboratory

R01-CA-28921 Merocyanine Dyes as Leukemia-Specific Probes
Robert A. Schlegel — Pennsylvania State University

R13-CA-29859 Eighth Conference on Analytical Cytology
Myron R. Melamed — Memorial Sloan-Kettering Institute for Cancer Research

R01-CA-30148 Development of Lanthanide Fluorescent Stains
Lidia M. Vallarino — Virginia Commonwealth University

R01-CA-30582 Multistage Slit-Scan Prescreening System
Leon L. Wheeless — University of Rochester Medical Center

4. PATHOLOGY

R01-CA-21905 Pituitary Adenomas: Structure-Function Relations
Calvin Ezrin — Cedars-Sinai Medical Center

R01-CA-22101 Study of Head and Neck Cancer by Serial Section
John A. Kirchner — Yale University

R01-CA-23922 Breast Cancer
Thomas G. Pretlow — University of Alabama in Birmingham

R01-CA-26422 Clinico-Biologic Correlation in Lymphoma and Leukemia
Henry Rappaport — City of Hope National Medical Center

5. RADIOLOGICAL IMAGING

R01-CA-15882 Transverse Section X-Ray Camera
Gordon L. Brownell — Massachusetts General Hospital

R01-CA-16543 Investigation of Charge Transfer Electroradiography
Ivor Brodie — SRI International

R01-CA-19787 Low Dose Breast Electron Radiography (Ionography)
Gary S. Shaber — Thomas Jefferson University

R01-CA-23246 Recognition of Very Small Tumors
Tamas Sandor — Harvard University

R01-CA-23816 Optical Quality Effects on Lung Tumor Detection
Robert D. Moseley, Jr. — University of New Mexico

R23-CA-23818 Image Reconstruction from Incomplete Projections
Robert M. Lewitt — State University of New York at Buffalo

R01-CA-24625 Diagnostic Accuracy and X-Ray Image Properties
George Revesz — Temple University

R01-CA-24806 Radiographic Imaging for Cancer Diagnosis
Kunio Doi University of Chicago

R01-CA-24822 3-D Tomogram Viewer for Cancer Detection and Therapy
Brent S. Baxter University of Utah

R23-CA-24879 Malignant Perfusion: Applied to Diagnosis and Therapy
Stuart Young Stanford University School of Medicine

R23-CA-25372 New Fluorescent X-Ray Tubes for Mammography
G. Allan Johnson Duke University

R01-CA-26327 Test Phantoms for Optimizing Mammographic Techniques
Leonard Stanton Hahnemann Medical College and Hospital

R01-CA-27823 A Scanning Equalization System for Chest Radiography
Donald B. Plewes University of Rochester

R01-CA-27875 Post-Mortem X-Ray and Histology of Sella and Pituitary
Dennis D. Spencer Yale University

R01-CA-29171 Integral and Mean Dose in CT Examinations
Feargus O'Foghludha Duke University School of Medicine

R01-CA-31217 New Reconstruction Algorithms for Computed Tomography
Robert M. Lewitt University of Pennsylvania

6. NON-RADIOLOGICAL IMAGING

R01-CA-15300 Application of NMR Zeugmatography in Cancer Research
Paul C. Lauterbur State University of New York at Stoney Brook

R01-CA-19019 Ultrasound Mammography
Gilbert Baum Yeshiva University - Albert Einstein College of Medicine

R01-CA-24085 Breast Diagnosis Quantitative Imaging by Ultrasound
James F. Greenleaf Mayo Foundation

R01-CA-24257 Breast Tumor Diagnosis by Computed Ultrasound
William Swindell University of Arizona

R01-CA-25323 Ultrasonic Computed Tomography of Breast Cancer
Paul L. Carson University of Colorado Medical Center

R01-CA-25634 Development of Ultrasonic Breast Tissue Phantom
James A. Zagzebski University of Wisconsin

R01-CA-25938 Scanning Acoustic Microprobe for Cancer Diagnosis
Frank E. Barber Harvard University

R01-CA-27021 Heavy-Ion Radiography and Cancer
Cornelius A. Tobias University of California Berkeley

R01-CA-27895 Transpelvic Ultrasound Evaluation of the Prostate
Aubrey M. Palestrant Beth Israel Hospital

R01-CA-28873 Non-invasive Sensing of Subcutaneous Temperatures
Alan H. Barrett Massachusetts Institute of Technology

P01-CA-28881 Evaluation of High Field Medical NMR Imaging
Sadek K. Hilal Columbia University

7. NUCLEAR MEDICINE

R01-CA-08349 Potential Tumor or Organ Imaging Agents
Raymond E. Counsell University of Michigan at Ann Arbor

R01-CA-16861 Bifunctional Chelating Agents in Tumor Localization
Claude F. Meares University of California Davis

R01-CA-17742 Radiological Localization of Human Tumors
James F. Primus University of Kentucky

R01-CA-18153 Cancer Studies with New Radioactive Scanning Compounds
John S. Laughlin Sloan-Kettering Institute for Cancer Research

R01-CA-19898 Synthesis of New ^{75}Se Organ Specific Imaging Agents
Michael A. Davis Northeastern University

R01-CA-22464 Gallium (III) Complexes in Aqueous Solution
Arthur E. Martel Texas A & M University

R01-CA-22578 Melanoma Delineating Radiopharmaceuticals
Ned D. Heindel Hahnemann Medical College and Hospital

P01-CA-23417 Improved Tumor Imaging in Nuclear Medicine
Harrison H. Barrett University of Arizona

R23-CA-24344 Synthesis, Chemistry of Technetium Radiopharmaceuticals
Michael J. Clarke Boston College

R01-CA-24597 Melanoma Detection with Radiopharmaceuticals
Harold L. Atkins Brookhaven National Laboratory

R01-CA-26371 Radiopharmaceuticals for Positron Tomography in Cancer
David R. Elmaleh Massachusetts General Hospital

R01-CA-26968 Improved Tumor Imaging with New Radioactive Liposomes
Donald J. Hnatowich University of Massachusetts Medical School

R01-CA-27252 Metabolism of Bone Scanning Radiopharmaceuticals
Charles D. Russell University of Alabama in Birmingham

R01-CA-28105 An Electronically Collimated Gamma Tomography System
Manbir Singh University of Southern California

R01-CA-28343 Bifunctional Chelates in Cancer Imaging and Therapy
David A. Goodwin V.A. Medical Center

R01-CA-28561 Development of Tumor and Organ Imaging Agents
Larry A. Spitznagle University of Maryland at Baltimore

8. MULTIPLE DISCIPLINES

R01-CA-25582 Fluorescence Endoscopy and Photoradiation Therapy
Oscar J. Balchum University of Southern California

CONTRACT RESEARCH SUMMARY

Title: Contrast Agents in Detecting Liver Metastases with Computerized X-ray Tomography

Principal Investigator: Dr. Michael A. Davis
Performing Organization: Brigham & Women's Hospital
City and State: Boston, MA

Contract Number: NO1-CB-84234
Starting Date: 7/01/78 Expiration Date: 6/30/81

Goal: To improve detection of small metastatic lesions in the liver by improved use of contrast agents to provide appropriate image enhancement in x-ray computerized tomographic studies.

Approach: The work, which will be carried out over a three-year period, will consist of six tasks: synthesis of new hepatic-specific contrast agents; preliminary evaluation in animal models; toxicity evaluation in animals; pilot clinical studies with currently available contrast agents; pilot clinical studies of promising new agents with acceptable toxicity characteristics; and clinical trials on the most promising contrast agent.

Progress: Work has progressed in two major areas:

1) Non-metabolizable reticuloendothelial (RE) tissue imaging agents.

Acute toxicity trials of cerium oxide indicate that there is no acute toxicity at doses anticipated to provide 50 Hounsfield Units (HU) of contrast enhancement of the normal liver. Extensive sub-acute toxicity testing is under way, prior to human clinical trials.

2) Development and testing of metabolizable RE tissue agents.

A. Radiopaque liposomes - Two varieties of radiopaque liposomes (phospholipid vesicles) were created. Those made from egg yolk lecithin, cholesterol, and stearylamine in a 4:1:1 molar ratio and carrying meglumine and sodium diatrizoate demonstrated prolonged blood pool opacification and clearance through reticuloendothelial tissues. Contrast enhancement of the heart, vessels, liver, and spleen was recognized. Contrast enhancement of these tissues was prolonged. At 10 minutes, nearly 30% of the injected dose was still present in the blood pool, only falling to 23% at 60 minutes. Maximal measured contrast enhancement of the blood was 116 HU, the liver enhanced 62 HU, and the spleen 87 HU, following a radiopaque liposome dose that contained 190 mg iodine. These peak levels were nearly sustained for 60 minutes and slowly decreased to base line levels over one day. There was strikingly greater opacification of all of these structures than provided by an equivalent amount of iodine in Renografin.

Additional studies on materials prepared from soy bean lecithin, cholesterol, and stearylamine in 8:1:1 molar ratio showed that this material went predominantly to the spleen. Peak spleen numbers were consistently greater than 100 HU following doses of 33:3 mg I in radiopaque liposomes.

B. Radiopaque albumin - Synthesis of radiopaque, iodinated albumin has been accomplished. This material is currently being tested in animals to assess its biodistribution.

Project Officer: Dr. Bill Bunnag
Program: Diagnosis
FY 81 Funds: $293,000

CONTRACT RESEARCH SUMMARY

Title: Digital Image Processing Techniques in Cytology Automation

Principal Investigator: Dr. Kenneth R. Castleman
Performing Organization: JPL-California Institute of Technology
City and State: Pasadena, CA

Contract Number: YO1-CB-70314
Starting Date: 9/19/77 Expiration Date: 9/30/81

Goal: Identification of the best performing image analysis algorithms and estimations of the expected performance and cost per specimen of an automated cervical cancer pre-screening system using these algorithms.

Approach: The contractor shall determine whether or not the current state of the art in pattern recognition is adequate to support the development of an economically viable cytological screening instrument based on single cell classification. Specimen preparation protocol will be optimized so as to produce acceptable single cells for digitization. A large number of digitized images will be accumulated in a library for a subsequent feature extraction program to produce a feature data base. A series of classification experiments will be run on the feature data base to select the subset of cell measurements that yield the best overall performance. An analysis will produce estimates of the cost and performance using these techniques in practice.

Progress: A new specimen preparation protocol has been developed. Over 10,000 digitized cell images were acquired and classification algorithms were developed and tested. New statistical methods for optimal specimen classification and analysis have been developed. The analysis of a cascade of a cell classifier followed by a specimen classifier has provided quantitative criteria for evaluating all classifier effectiveness as part of an overall system. This analysis has also provided guidelines for tuning the parameters of the cell classifier. A cost/utility analysis has indicated that the cell classification algorithms chosen can operate with error rates that are adequate for routine screening.

The second phase of the study has been initiated. This phase will evaluate the performance of the cell classification algorithms on cells selected and segmented without human intervention. New algorithms for fully automatic cell finding and segmentation have been developed, and are undergoing test and evaluation.

Project Officer: Dr. Bill Bunnag
Program: Diagnosis
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Diagnostic Application of Monocyte Function in Cancer

Principal Investigator: Dr. Ralph Snyderman
Performing Organization: Duke University Medical Center
City and State: Durham, NC

Contract Number: NO1-CB-74121
Starting Date: 9/30/77 Expiration Date: 6/29/81

Goal: To determine the significance of abnormal monocyte functions in humans with cancer.

Approach: The relationship between the clinical status of cancer patients and their monocyte function in vitro is being determined. Parameters of phagocytic cell function such as chemotactic responsiveness, phagocytosis, superoxide production and chemotactic factor binding are being examined. We seek to determine the significance of the depression of monocyte chemotaxis which has been found in cancer patients. The effect of tumor removal in phagocytic cell function is being examined. The effects of effusions from patients with various types of cancer on the function of normal monocytes are also being examined.

Progress: We have previously demonstrated that monocyte chemotactic responsiveness in vitro is depressed in approximately 60% of patients with cancer. Removal of the tumor by surgery or by immunotherapy reverses this defect, suggesting that tumor associated factors might be responsible. Using a newly developed assay for measuring one of the early responses of monocytes to chemotactic stimuli, i.e., the change in shape from round to an elongated, polarized configuration, we are now examining fluids from patients for the presence of soluble inhibitors of chemotactic responses. We have found inhibitory activity for monocyte polarization in the fluids of all (22/22) of the cancer patients studied thus far, representing 15 different tumor types, but in none of 17 fluids from patients with non-malignant diseases. Fractionation of fluids by high pressure liquid chromatography revealed three peaks of inhibitory activity: $\geq$ 200,000 daltons; 46,000 $\pm$ 13,000 daltons; and 21,000 $\pm$ 3,000 daltons. The inhibitory activity was shown to be heat stable (56°C, 30 min) and trypsin-sensitive. Three different monoclonal antibodies to the P15(E) structural component of murine type C retroviruses were capable of absorbing the inhibitory activity from all eight fluids tested while six other monoclonal antibodies had no effect. We are currently in the process of further characterizing this inhibitory material and screening for its presence in the serum of cancer patients.

Project Officer: Dr. Bernice T. Radovich
Program: Diagnosis
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Screening for Medullary Carcinoma of the Thyroid

Principal Investigator: Dr. Samuel A. Wells, Jr.
Performing Organization: Duke University Medical Center
City and State: Durham, NC

Contract Number: NO1-CB-63994
Starting Date: 6/15/76 Expiration Date: 6/14/81

Goal: To establish a periodic screening program of relatives of patients with medullary thyroid carcinoma (MTC).

Approach: A cohort of patients comprised of seven kindreds in which MTC is proven histologically will be established and be large enough to offer a statistically significant number of family members. Those family members will be screened for serum calcitonin levels by radioimmunoassay methods in order to detect MTC in its earliest stage of development. A long-term follow-up program will be conducted in these families to determine the natural history of the disease and the effectiveness of surgical and possible chemical therapy.

Progress: Our study of approximately 800 subjects from 13 kindreds with multiple endocrine neoplasia, type II (medullary thyroid carcinoma (MTC), pheochromocytoma and hyperparathyroidism) has completed its fifth year. We have demonstrated that the combined infusion of calcium gluconate (2 mg/kg/1 min) followed by pentagastrin (0.5 μg/kg/5 sec) is the most sensitive method of stimulating calcitonin (CT) release from MTC cells. This combined infusion serves as the most efficient method for establishing the early diagnosis of MTC. Over the last year we have identified two kindreds who inherit only MTC with none of the extrathyroidal manifestations of multiple endocrine neoplasia (MEN), types IIa or IIb. Furthermore, the MTC in these patients appears to be less aggressive than the MTC occurring in subjects with MEN IIa or subjects with MEN IIb.

Also, over the last year, Dr. Stephen Baylin and associates at the Johns Hopkins Hospital have utilized immunoperoxidase techniques for determining calcitonin content in primary MTC. It has been learned that patients whose tumors stain heterogenously with calcitonin have a relatively poor prognosis compared to those whose tumors demonstrate homogenous calcitonin staining. We are conducting further experiments to define the utility of this prognostic indicator.

We continue to evaluate chemotherapeutic agents in the treatment of patients with metastatic MTC. Thus far, of several chemotherapeutic agents, none has proven of benefit with the possible exception of adriamycin in two patients.

Project Officer: Mr. Louis P. Greenberg
Program: Diagnosis
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Data Management System for NCI Serum Panels

Principal Investigators:	Dr. Lee A. Richman, Dr. C. M. Dayton
Performing Organization:	Ebon Research Systems
City and State:	Washington, DC

Contract Number:	N01-CB-74210		
Starting Date:	8/08/77	Expiration Date:	8/07/82

Goal: To provide data management and statistical programming support for research projects being conducted by the Diagnosis Program in order to determine which serum tests are best able to detect early stages of cancer.

Approach: To perform statistical analyses of data from NCI serum panel evaluations and to prepare summary reports of the results.

Progress: Approximately two serum panels have been forwarded to us each month, and we have conducted the following statistical analyses on each:

(1) The production of plots, such as histograms, so the distributions across clinical groups can be compared. In most instances an analysis of variance accompanies each plot.

(2) Chi-square (2 x 2) tables for a variety of clinical comparisons. Accompanying each chi-square value are the associated two-tailed probability, sensitivity, specificity, and number of misclassifications for the comparison. When cut-scores separating positive from negative groups are found by inspection of the data--minimizing the number of misclassifications--a Kolmogorov-Smirnov statistic is used instead of chi-square.

(3) McNemar chi-square tests, when appropriate, to determine whether the rates of positive classifications are the same for two assays.

(4) Discriminant analyses for multiple comparisons to combine information from the assays into a single prediction function.

(5) Gail-Green procedures for locating optimal cutting scores.

(6) Scattergrams for pairs of assays.

In general, none of the panels analyzed since September 1, 1980 (including a large comparative analysis of assays of immune complexes) were adequate in their ability to discriminate between cancer and non-cancer cases.

Project Officer: Dr. Bernice T. Radovich
Program: Diagnosis
FY 81 Funds: $76,000

CONTRACT RESEARCH SUMMARY

Title: Immunodiagnostic Markers for Breast Cancer

Principal Investigator: Dr. Rajender K. Chawla
Performing Organization: Emory University
City and State: Atlanta, GA

Contract Number: NO1-CB-84308
Starting Date: 9/30/78 Expiration Date: 9/29/81

Goal: To evaluate urinary/plasma levels of EDC1, the principal component of cancer-related proteinuria, as an immunodiagnostic marker for breast cancer.

Approach: Pure EDC1 and inter-α-trypsin inhibitor (IATI) and high titer antiserum to EDC1 will be prepared. Standardized immunologic methods (e.g., radioimmunoassay (RIA) or immunoelectrophoretic techniques) will be developed to monitor EDC1 in urine/plasma of i) normal healthy women; ii) women with metastatic breast cancer; iii) patients with non-neoplastic diseases; and iv) preoperative patients with localized breast mass. A postoperative longitudinal study will monitor EDC1 levels of patients in group iv with malignant lesions.

Progress: A novel glycoprotein EDC1, MW 27.5 K, isolated originally from urine of a leukemic patient was found to be immunologically related to a normal plasma protein, IATI (MW 170 K). Urinary EDC1 levels have been measured in the above four groups of subjects. The ave $\pm$ SEM values (mg/g urinary creatinine) were as follows: i) normal women: 8.0 $\pm$ 2.2 and ii) metastatic breast cancer patients: 98.6 $\pm$ 11. Sixty-six out of 82 patients with noncancer diseases had an ave EDC1 level of 14.6 $\pm$ 4; the remaining had an ave of 94.8 $\pm$ 16. Among the latter subgroup were patients with renal failure, rheumatoid arthritis, and infectious diseases. The immunoreactive material excreted in these non-cancer diseases was of higher MW (presumably IATI) and was positively correlated with the degree of renal insufficiency. In the 26 preoperative patients, subsequently shown to have benign lesion, the average EDC1 excretion was 21.5 $\pm$ 3.4; 24 of these patients were in the normal (<15 mg) to light (15-30 mg) range and 2 were in the intermediate (31-45 mg) range. In the other preoperative subgroup (25 patients) subsequently shown to have malignant lesions, the ave EDC1 excretion was 43.1 $\pm$ 7.6 mg, with 8 normal, 5 light, 4 intermediate and 8 heavy (>45 mg) excretors. Clinical evaluation of preoperative patients with malignant lesions and its correlation with EDC1 levels showed a direct correlation between the number of nodes and the level of EDC1. Postoperative follow-up in the heavy excretor preoperative patients showed a marked decline in EDC1 following removal of the tumor (from 171 to 21 mg). Analyses of fractions obtained by gel filtration of plasma of metastatic breast cancer patients showed no significant accumulation of EDC1, suggesting rapid clearance of EDC1 from plasma. Preliminary data indicate that total IR-IATI in breast cancer is about 2/3 of that in the normals.

Project Officer: Dr. Bernice T. Radovich
Program: Diagnosis
FY 81 Funds: $41,783

CONTRACT RESEARCH SUMMARY

Title: Clinical Evaluation of Immunodiagnostic Tests for Cancer

Principal Investigator: Dr. Adly N. Ibrahim
Performing Organization: Georgia State University
City and State: Atlanta, GA

Contract Number: NO1-CB-84267
Starting Date: 2/01/78 Expiration Date: 6/30/81

Goal: Immunodiagnosis of cervical and head and neck cancers.

Approach: Antisera are prepared in rabbits against cervical cancer tissues. Elimination of antibodies against normal tissues and normal human sera is carried out by various methods. These antisera will be used for the detection of circulating tumor-associated antigens (C-TAA) in sera of patients with cervical and head and neck cancers. Serum controls including those from normal individuals and from patients with benign diseases of these sites will be used.

Progress: The contractor has purified hyperimmune sera against partially purified cervical cancer tumor-associated antigens (CaCx TAA) using ion exchange and affinity chromatography. These antisera were evaluated for the detection of C-TAA in sera from cervical cancer patients using an indirect method of enzyme-linked immunosorbent assay (ELISA) as well as the immunodiffusion technique (ID). ELISA has increased significantly the detection of C-TAA. Specificity was high though not absolute. Efforts will continue to increase the sensitivity and specificity of ELISA. Preparation of monoclonal antibodies against CaCx TAA's has been initiated using hybridomas. Such antibodies will be used for (1) immunodiagnosis of cervical and head and neck cancers using ELISA and RIA. It is expected that such antibodies will increase the specificity of the tests, and (2) to study the TAA fractions obtained after purification of CaCx TAA's. Antisera prepared against a continuous cell line derived from cervical cancer tissues using immunodiffusion adsorption-in-gel technique. Using coded human sera in blind tests, anti-C_4II sera detected C-TAA in 24/36 (66.6%) sera from patients with cervical cancer. Five of 126 (3.9%) control sera gave false positive reactions. This continuous cell will also be used to purify C_4II TAA's, and to prepare monoclonal antibodies. Preliminary results indicate that CaCx TAA's and C_4II TAA's may be identical. Studies indicated the presence of at least 3 CaCx TAA's. Purification, isolation and characterization of each TAA are pursued actively. During the progress of the hybridoma work, hyperimmune mouse sera and ascitic fluids against CaCx TAA's were evaluated for diagnosis of cervical cancer using ELISA. Results indicated that the mouse antibodies are superior and more specific than those of rabbits for this purpose.

Project Officer: Dr. Bernice T. Radovich
Program: Diagnosis
FY 81 Funds: $20,835

CONTRACT RESEARCH SUMMARY

Title: Immunologic Markers Applicable to Cytology Automation

Principal Investigator: Dr. Laure Aurelian
Performing Organization: Johns Hopkins University
City and State: Baltimore, MD

Contract Number: NO1-CB-74170
Starting Date: 7/18/77 Expiration Date: 7/27/81

Goal: To study qualitative and quantitative antigenic changes in premalignant and malignant cells.

Approach: The contractor shall isolate HSV antigens: (i) total HSV-2 antigens, (ii) total HSV-1 antigens, (iii) AG-e, (iv) AG-4/ICP 10 and prepare corresponding purified antisera. The contractor shall also attempt to obtain antiserum to VP143 from an independent investigator. The sera will be used to stain human gynecologic specimens in indirect immunofluorescence. The sensitivity and specificity of these antisera in terms of their ability to discriminate premalignant and malignant cells from normal cells will be determined.

Progress: AG-e purified by crossed immunoelectrophoresis has been resolved by SDS acrylamide gel electrophoresis into two component proteins designated ICP 12 (MW 140,000) and ICP 14 (MW 130,000). Antisera were prepared against AG-e, ICP 12 and ICP 14 and their reactivity determined. ICP 12 and ICP 14 appear to be virion envelope proteins.

In indirect immunofluorescence, antisera to AG-e, ICP 12 and ICP 14 stain exfoliated atypical but not normal cells. In a double blind study designed to compare immunofluorescent markings of specimens by antiserum to AG-e, a very good correlation (80-93.8%) was observed between staining with anti-AG-e serum and routine manual screening. Very good correlation is observed in ongoing blind studies (including specimen by specimen and cell by cell comparisons) between the staining potential (frequency of positive patients and percent of positive cells/patients) of antisera to total HSV-2 antigens, to total HSV-1 antigens and to AG-e. However, antisera to ICP 12 and ICP 14 stain a smaller number of cells and a lower frequency of patients are responsive. Presently ongoing studies indicate that reactivity with antiserum against AG-4/ICP 10 reflects the progression of the cervical lesion. Thus 4/10 patients with mild dysplasia, 7/10 with moderate dysplasia and all those with a lesion diagnosed as, at least, marked dysplasia had AG-4/ICP 10 positive cells. Normal cells from these patients and normal control women were negative.

Project Officer: Dr. Bill Bunnag
Program: Diagnosis
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Lung Cancer Control: Detection and Treatment

Principal Investigator: Dr. John K. Frost
Performing Organization: Johns Hopkins University
City and State: Baltimore, MD

Contract Number: NO1-CN-45037
Starting Date: 1/01/73 Expiration Date: 7/15/81

Goal: To determine the effect on mortality from lung cancer of early detection of this disease by sputum cytology followed by surgical removal of the tumor.

Approach: The study population consists of males who, at the time of enrollment, were 45 years or older and had smoked a pack or more of cigarettes a day. Individuals responding to invitation, by direct mailing and other means, were randomly assigned to one of two groups: the "X" group receives an annual chest x-ray only; the "CX" group receives an annual chest x-ray, an annual sputum induction plus a sputum cytologic examination every four months. Subjects suspicious or positive for cancer are carefully evaluated, including localization of the cancer by fiberoptic bronchoscopy. Cancers are removed surgically when possible. All subjects will be followed for at least 5 years after final screening to determine actuarial survival.

Progress: A total of 10,387 men have been enrolled in this project, of which 5,161 were randomized into the "X" group and 5,226 into the "CX" group. To date, 740 have died, while 1,669 have withdrawn from the study or moved from the area. Currently 7,978 remain as active participants, 4,025 in the "X" group and 3,953 in the "CX" group. At the initial screening 78 cancers were detected (40 in the X group and 38 in the CX group) for a "detected prevalence" of 7.5 per 1,000. Following an initial negative screening, a total of 200 cancers appeared (102 in the X group and 98 in the CX group) for an "annual incidence" of 4.7 per 1,000. In the CX group, 37 (65%) incidence cases were detected at AJC Stage I (localized), 10 (27%) of these were in situ and 27 (73%) invasive; 41 additional cases occurred between screenings, 15% at Stage I. In the X group, 32 (51%) incidence cases were detected at AJC Stage I, all invasive; 39 additional cases occurred between screenings, 21% at Stage I. Among the 98 cases occurring in the CX group after initial screening, 46 (47%) were resected; 45 (44%) of the 102 incidence cases occurring in the X group were resected. In the screened population, 278 total lung cancers have appeared: 142 in the X group and 136 in the CX group. Among the 142 cases of lung cancer found in the X group, 86 (61%) have died; of the 136 lung cancer cases in the CX group, 66 (49%) have died. Lung cancer mortality has not yet been shown to be significantly different between the CX (30 per 10,000 person-years) and X (41 per 10,000 person-years) groups, nor has a significant difference been shown yet from that expected from application of the age and smoking specific lung cancer mortality rates of historical control groups.

Project Officer: Dr. Bill Bunnag
Program: Diagnosis
FY 81 Funds: $760,000

CONTRACT RESEARCH SUMMARY

Title: Immune Assays for Enzymes and Isozymes in Cancer

Principal Investigator: Dr. Joel H. Shaper
Performing Organization: Johns Hopkins University
City and State: Baltimore, MD

Contract Number: NO1-CB-84260
Starting Date: 9/22/78 Expiration Date: 9/21/81

Goal: Development of immunodiagnostic assays for cancer using an enzyme or isozyme as an antigen and to look for a correlation of enzyme/isozyme serum levels with tumor burden.

Approach: Evaluate the immunodiagnostic significance of serum levels of UDP-galactosyltransferase in human breast and ovarian carcinoma.

Progress: Antisera directed against affinity-purified bovine UDP-galactosyltransferase have been prepared in rabbits and partially immunologically characterized. These antisera have relatively high titered precipitating antibody to bovine galactosyltransferase as assessed by the Ouchterlony double diffusion technique and inhibition of enzymatic activity. The antisera are highly cross-reactive with human UDP-galactosyltransferase found in both normal serum and ascitic fluid obtained from a patient with ovarian cancer as determined by direct precipitation and inhibition of enzymatic activity. This cross-reactivity has been exploited for the development of a sensitive and specific radioimmunoassay for human serum UDP-galactosyltransferase with a detection level of 0.1-1.0 nanograms in the assay mixture.

Work during the last 6 months has been focused on two areas: one, setting up and debugging of the NIH RIA data processing program which has been initiated to store and manipulate the data and two, performing a retrospective clinical study in which serum GT levels were quantitated by RIA on a limited number of patients with Stage IV breast carcinoma. These samples were initially collected and GT levels measured by kinetic assay. In this limited study, the GT levels were quantitated by the newly developed RIA and were in good agreement with the quantitation by kinetic assay. A more systematic and comprehensive study has been initiated to determine the degree of correlation of human serum GT levels with tumor burden, stage of disease, response to therapy, and progression of tumor growth.

Project Officer: Dr. Bernice T. Radovich
Program: Diagnosis
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Clinical Evaluation of Immunodiagnostic Tests for Cancer

Principal Investigator: Dr. John Fenimore Cooper
Performing Organization: Kaiser Permanente Medical Group
City and State: Los Angeles, CA

Contract Number: NO1-CB-74169
Starting Date: 9/16/77 Expiration Date: 7/15/81

Goal: Evaluation of radioimmunodiagnostic tests for prostatic cancer.

Approach: Accumulation and assessment of clinical oncologic data for prostatic cancer with a solid phase radioimmunoassay technique for prostatic acid phosphatase (RIA-PAP); continuing development of the RIA-PAP technique as a potential screening population of elderly males over the age of 50 years at risk for the disease.

Progress: Analysis of the data obtained from the screening study of nearly 6,000 men was continued with the following new findings. (1) In normal individuals the mean RIA value obtained is independent of age. This implies that no age adjustment of the RIA value is required in clinical practice. (2) In individuals with benign prostatic hypertrophy (BPH) a similar invariance of the RIA value with age is observed. Thus, no adjustment of the observed RIA value is necessary in interpretation of data in BHP patients. (3) The number of cases detected per 1,000 cases screened increases dramatically over the age of 65 years. These data should allow us to quantitatively limit any future screening to individuals in this age category. (4) A careful review of the clinical charts of individuals detected in the screening program demonstrates that some subjects had previously suspected or diagnosed history of prostatic disease. Most of these individuals demonstrated stage 4 disease at the time of the screening procedure. Exclusion of these individuals markedly shifts the stage distribution of detected disease to earlier stages (2 and 3). Therefore, the years of life saved by earlier detection of disease stages due to screening appears to be increased. Value of the screening procedure is greatly enhanced by these findings. Work currently in progress will provide detailed data description of individuals in the normal, BPH, and disease categories. Parameters of specificity and predictive value of a positive test will be examined. Finally, the value usually chosen to designate suspicion of disease (RIA value: 6.5 mg/ml) will be varied between 7 and 10, and the impact of such changes on specificity and predictive value will be examined.

Project Officer: Dr. Bernice T. Radovich
Program: Diagnosis
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Diagnostic Applications of Antibodies to Melanoma

Principal Investigator: Dr. Peter Hersey
Performing Organization: Kanematsu Institute
City and State: Sydney, Australia

Contract Number: NO1-CB-74120
Starting Date: 9/30/77 Expiration Date: 9/29/81

Goal: Determine whether there is a correlation between the clinical course of melanoma growth and levels of serum antibodies.

Approach: Employ lymphocyte-dependent cytotoxic antibody (LDA) assays.

Progress: During the first 39 months of this study, 414 patients with localized melanoma were studied. Of these, 228 had LDA activity detected against allogeneic cultured melanoma cells. In 139 patients a rise in LDA activity was noted after surgical removal of the melanoma followed by a gradual delay to undetectable levels by 2-3 months. Twenty-seven patients had detectable antibody to melanoma cells before removal of melanoma which remained unchanged after surgery. Twenty of the latter were multiparous women. Of the 248 patients with no antibody detectable in their sera, 62 had LDA activity detectable in the IgG fractions of sera obtained by gel filtration of acidified 'unblocked' sera. Sera from 23 of 124 patients with non-melanoma carcinoma had LDA activity to allogeneic melanoma cells. All but one of the sera from this latter group of patients also reacted with allogeneic cells from cell lines established from breast and bladder carcinoma and the Chang liver cell line and were not specific for melanoma. This contrasted with the results of studies on the melanoma patients in that 158 of the 228 positive sera did not react with cells from non-melanoma cultures. Studies on the specificities of these sera are in progress. Thirty-eight patients, studied at the time of initial presentation, have had recurrences. No significant differences in recurrence rate in relation to LDA status is yet apparent. Trends for a lower rate of recurrence in patients with high constant LDA are, however, apparent. Much longer follow-up periods are required before the importance of LDA in relation to recurrences from melanoma will be known.

Project Officer: Dr. Bernice T. Radovich
Program: Diagnosis
FY 81 Funds: $33,900

CONTRACT RESEARCH SUMMARY

Title: Innovative Techniques for Passage of Colonoscope

Principal Investigator: Dr. John A. Coller
Performing Organization: Lahey Clinic Foundation
City and State: Boston, MA

Contract Number: NO1-CB-74212
Starting Date: 9/26/77 Expiration Date: 9/25/81

Goal: To develop a means for improving early detection of cancer on endoscopically approachable surfaces of the colon in order to improve life expectancy.

Approach: A colonoscope advancing device will be developed to enhance the ease and speed of passage of currently available colonoscopes. Modeling studies and bench testing will be conducted during the initial year to determine which of several possible designs may be feasible. Further development of the colonoscope advancing device design will be carried out during the second year aided by physiological studies made to characterize as many physical parameters of the human colon as possible. Suitable devices will be given preliminary clinical tests during the latter part of the second year. After further optimization the clinical prototype propulsive devices will be tested by clinical trials in the third year.

Progress: During the first year, efforts were directed towards defining and measuring physiologic characteristics of colon function that relate to the intubation problem. From these observations, together with a mathematical modeling approach, various bench models were developed for testing discrete aspects of the problem. The various techniques in the construction of fibroelastomeric structures were developed. During the second year, fibroelastomeric structures of various configurations were constructed and submitted to both bench and animal testing. A major problem which became apparent at this point was the disparity between the various bench models and the more compliant animal colon. Consequently, the major effort during year three has been to use the animal preparation as the main evaluatory system with fibroelastomeric devices that are designed to accept rather than combat the compliant nature of the colon. At present, suitable fibroelastomeric constructions are being prepared for preliminary evaluation in humans.

The structural configuration of the surface envelope has been altered in order to minimize the longitudinal as well as torsional resistance. The axial driving concept has been replaced by a torsional mechanism directed at a random lumen-seeking tip. Further experimental study as well as trial human application is anticipated during year four.

Project Officer: Dr. Bill Bunnag
Program: Diagnosis
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Detection and Localization of Early Lung Cancer

Principal Investigator: Dr. Robert S. Fontana
Performing Organization: Mayo Foundation
City and State: Rochester, MN

Contract Number: NO1-CB-53886
Starting Date: 9/27/74 Expiration Date: 9/26/81

Goal: To test new methods of diagnosis of early lung cancer and to assess survival of patients with lung cancer detected by these methods.

Approach: A study population of 9,211 subjects was obtained following initial screening of 11,001 non-volunteers. Candidates were Mayo Clinic outpatients who were men, 45 years old or more, smoking one pack of cigarettes or more daily. None of those accepted into the study had a history or suspicion of respiratory cancer on entry into the Clinic; all had a life expectancy of at least 5 years, and all were judged capable of tolerating pulmonary resection (at least lobectomy). Initial screening consisted of chest radiographs, 3-day sputum cytology tests and lung health questionnaires. This screening yielded 91 unsuspected ("prevalence") lung cancers, 17 detected by cytology alone, 59 by radiography alone, and 15 by both tests. Radiographically "occult" cancers were localized fiberbronchoscopically. The 9,211 study subjects who had "negative" initial screens were randomized into a close-surveillance group, for whom rescreening every 4 months was urged, and a standard surveillance ("control") group advised, but not reminded, to undergo rescreening once a year. A population of post-surgical AJC stage I lung cancer patients is also being evaluated, as are hematoporphyrin derivative (HpD) and cryotherapy as techniques for "mapping" and treating carcinoma-in-situ.

Progress: As of April 1, 1981, the 4-monthly surveillance group and the "control" group had been observed more than 27,000 man-years, and 302 new ("incidence") cases of cancer of the respiratory tract had been detected, 63 involving the upper airway and 239 the lungs. In the 4-monthly surveillance group there were 135 new cancers (14 of which were detected by cytology only) and 68 lung cancer deaths. Survival data in this group are encouraging. In the control group there were 104 new lung cancers and 68 lung cancer deaths, with a tendency toward more traditional lung cancer survivorship. Thus, once lung cancer has been detected, survival in the 4-monthly surveillance group is considerably better than among the controls. So far there has been no decrease in total deaths from lung cancer in the close-surveillance group compared to the control group. Prolonged follow-up is essential before final conclusions and specific recommendations can be made. As "incidence" cases continue to accrue, more detailed analyses of data are feasible. Attention is currently directed toward evaluating the results of screening by cell type of tumor and by modality of detection. The post-surgical AJC stage I lung cancer study indicates that about 70% of those with non-small cell cancer survive 5 years. The HpD study has detected several squamous cancers that were both radiographically and endoscopically occult. Cryotherapy continues to be used in selected cases.

Project Officer: Dr. Bill Bunnag
Program: Diagnosis
FY 81 Funds: $650,000

CONTRACT RESEARCH SUMMARY

Title: Carcinoembryonic Antigen in the Diagnosis of Bowel Cancer

Principal Investigator:	Dr. Vay Liang W. Go
Performing Organization:	Mayo Foundation
City and State:	Rochester, MN

Contract Number:	NO1-CB-23854		
Starting Date:	6/15/72	Expiration Date:	6/14/82

Goal: To determine the usefulness of CEA in the diagnosis of bowel cancer.

Approach: (a) Measure CEA levels in blood and other specimens stored at NCI-Mayo Clinic Human Serum Bank (CB-84258), Mayo Lung Cancer Project (NCI-CB-22000) and other contracts with the Diagnosis Program of the Division of Cancer Biology and Diagnosis; (b) continue to collect and provide colonic malignant tissue for different investigators in projects dealing with carcinoembryonic antigens; (c) complete the work done over the last five years in the continuation of the evaluation of CEA as a biologic marker in patients undergoing chemotherapy, radiotherapy, and immunotherapy of advanced gastrointestinal cancer.

Progress: (a) Progress related to the contract's service function activity. Serum or plasma levels have been determined in 7,984 specimens from NCI Serum Plasma Bank including those sent in from other investigators. These samples were run at 20% of the commercial cost. Comparative studies with other methodologies for measuring CEA including the enzyme immunoassay were carried out. The comparison of values of CEA to other tumor-associated antigens was done with investigators from other institutions and has resulted in several publications. Statistical analyses of the data over the last three years were included in the Workshop on Immunodiagnosis of Human Cancer, Statistical Analyses, Part II. Results and statistical analyses are being performed on coded serum panels which were sent last year to 17 investigators with potentially useful diagnostic tests for cancer.

(b) Progress report on the evaluation of CEA as a biological marker. Data are still being collected for the evaluation of CEA as a biologic marker in patients following resection of gastrointestinal cancer with curative intent, in patients undergoing chemotherapy, radiotherapy and immunotherapy for advanced gastrointestinal cancer and in lung cancer patients. Preliminary data have been analyzed for publication purposes.

Project Officer: Mr. Louis P. Greenberg
Program: Diagnosis
FY 81 Funds: $49,500

CONTRACT RESEARCH SUMMARY

Title: Maintenance of the NCI Serum Diagnostic Bank

Principal Investigator: Dr. V. L. W. Go
Performing Organization: Mayo Foundation
City and State: Rochester, MN

Contract Number: NO1-CB-84258
Starting Date: 9/30/78 Expiration Date: 6/30/81

Goal: To establish and maintain a bank of sera from patients with cancer, with benign diseases and from normal individuals, for evaluating immunodiagnostic tests of potential clinical usefulness in the diagnosis of cancer.

Approach: Make necessary serum samples available for evaluation of immunodiagnostic tests for cancer. Serve as a central facility for storage of serum and plasma specimens collected by other contractors in the Tumor Immunology-Immunodiagnosis Program.

Progress: In 1981 through April 1, 5,342 vials of sera were collected by the central facility for a total of 147,637. In 1981, 1,437 vials were shipped out to investigators for a total of 63,187. Presently there are 84,450 vials from the central facility and 160,701 vials from various screening projects for a total of 245,151 vials stored at the Mayo-NCI Serum Diagnostic Bank.

Project Officer: Dr. Bernice T. Radovich
Program: Diagnosis
FY 81 Funds: $85,810

CONTRACT RESEARCH SUMMARY

Title: Reconstruction Algorithms for Dose Reduction in X-Ray Computed Tomography

Principal Investigator: Dr. Richard A. Robb
Performing Organization: Mayo Foundation
City and State: Rochester, MN

Contract Number: NO1-CB-84235
Starting Date: 9/29/78 Expiration Date: 9/28/81

Goal: To develop and evaluate new and/or improved reconstruction methods directed toward reducing the x-ray dosage required to obtain diagnostically accurate information from CT scanning procedures used in cancer diagnosis.

Approach: A variety of approaches will be investigated for their contributions to improved image reconstruction with reduction in x-ray dosage. These will include studies for tailoring and optimizing convolution, least square, and iterative algorithms for low x-ray dose data; use of a priori information; noise reduction techniques; minimizing required field of view; non-linear spatial smoothing; and optimizing algorithms based on penalty functions and multiplier methods for constrained optimization. These methods will be tested on realistic mathematical simulations and on actual patient CT scan data. The results will be quantitatively evaluated using standard image quality measurement criteria and by comprehensive psychophysical (ROC) studies.

Progress: Different types and versions of reconstruction methods have been compared. Preliminary results in the use of positivity constraints indicate improvements in accuracy and speed of convergence for iterative type reconstructions but questionable effects for convolution methods. The maximum entropy algorithm has been applied to simulated low dose CT data containing complex lesions in uniform fields. Evaluation of the reconstruction has not confirmed the notion that such an algorithm is more effective than others in reducing the number of "false positives." Preliminary studies with algorithms for limited field of view indicate that relatively low contrast lesions are detectable and measurable in the field of view at low x-ray doses. Preliminary results with selective non-linear smoothing techniques indicate significant improvement in image signal-to-noise with potential for improvement in diagnostic quality. A survey of the field of optimizing algorithms has been prepared. Extensions of previously known methods for quadratic optimization have been produced. A preliminary ROC study has been performed on images of a realistic head phantom, with superimposed low-contrast "lesions," reconstructed using the standard convolution method on projection data generated with photon counts both typical of and considerably less than present day CT x-ray scanners. Two other algorithms have been selected for evaluation using these data--weighted least square and an iterative optimizing algorithm which combines notions of regularization, penalty functions, Bayesian and multiplier methods. These algorithms will also be applied to actual clinical CT data of patients with lesions.

Project Officer: Dr. Bill Bunnag
Program: Diagnosis
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Collection of Serial Serum Samples from Cancer Patients

Principal Investigator: Dr. Carl Feit
Performing Organization: Memorial Hospital for Cancer and Allied Diseases
City and State: New York, NY

Contract Number: NO1-CB-04350
Starting Date: 9/30/77 Expiration Date: 9/29/82

Goal: Collect serial serum specimens from cancer patients and benign disease controls for evaluation of potential immunodiagnostic tests for cancer.

Approach: Collect serial specimens from patients with melanoma, ovarian carcinoma, lung carcinoma, and Hodgkin's disease plus suitably matched patients with benign skin lesions, benign adnexal masses, a history of heavy smoking, and benign lymphadenopathy to serve as controls.

Progress: This contract is completing the fourth year of a program for collection of serial serum specimens from cancer and control patients for use in evaluating potential immunodiagnostic tests for cancer. A total of 277 patients have been entered, including 155 patients and 122 controls. By diagnosis, the respective figures for patient/control entry are: ovarian, 37/33; lung, 32/20; Hodgkin's disease, 55/34; and melanoma, 31/25. An average of 44 blood samples are collected monthly. The total number of samples in the collection to date is 1,537. The patient population projected for completion of study is 325. To achieve this population it is anticipated 110 patients will have to be recruited. Progress has been made in data entry and computer control of data. Consultations are under way relating to the epidemiologic soundness of the collection and biostatistical approaches for handling the data generated by testing are being developed. All serum samples have been tested this year for a single marker, lipid-bound sialic acid (LSA). These data are being used by the biostatisticians to probe the utility of the collection for evaluating new tumor markers.

Project Officer: Dr. Bernice T. Radovich
Program: Diagnosis
FY 81 Funds: $135,104

CONTRACT RESEARCH SUMMARY

Title: Lung Cancer - Early Detection, Localization and Therapy

Principal Investigator: Dr. Myron R. Melamed
Performing Organization: Memorial Hospital for Cancer and Allied Diseases
City and State: New York, NY

Contract Number: NO1-CN-45007
Starting Date: 9/01/73 Expiration Date: 7/31/81

Goal: To evaluate sputum cytopathology as a supplement to annual chest x-rays in detecting pulmonary neoplasms at an "early stage" and to evaluate the efficacy of techniques for prompt localization of radiologically occult lung cancer (e.g., before progression to x-ray positive); in general, to evaluate the efficacy of such screening to reduce lung cancer mortality.

Approach: Over a 3-year period, 5,000 test subjects and 5,000 control subjects have been entered into this study. Each subject will receive active screening for at least 5 years, all followed for at least an additional 5-year period. This will be conducted according to a protocol developed in conjunction with the Johns Hopkins University and the Mayo Foundation.

Progress: Recruitment for the Memorial Sloan-Kettering Cancer Center National Lung Program was completed in January 1978. Total enrollment is 10,040. Participants were randomly assigned to study group (A) (4,969), receiving annual chest x-rays and 4-monthly sputum; and to control group (B) (5,071) receiving annual x-rays only. There have been a total of 217 confirmed lung cancers identified so far, 105 in group A and 112 in group B. The principal mode of detection in the A group was by cytology in 19 cases, x-ray in 49 cases and both techniques in 12 cases. Of the 19 cases detected by cytology, 13 were Stage 0 or I; of the 61 cases detected by radiology (or radiology and cytology) in group A and the 72 cases detected by radiology in group B, a total of 133 cases; there were 65 in Stage I. There were 65 interval cancers diagnosed following symptoms or signs or by x-rays taken outside of the routine screening program; only 11 of these were Stage I, and 21 were oat cell cancers.

Among the 105 lung cancers appearing in group A, 30 were prevalence cancers for a prevalence rate of 6.0/1,000 and 75 were incidence cancers for an incidence rate of 3.0/1,000/year. In group B the 112 lung cancers included 23 prevalence for a prevalence rate of 4.6/1,000 and 89 incidence cases, for an incidence rate of 3.5/1,000/year.

Project Officer: Dr. Bill Bunnag
Program: Diagnosis
FY 81 Funds: $900,000

CONTRACT RESEARCH SUMMARY

Title: Evaluation of Screening Methods for Endometrial Cancers

Principal Investigator: Dr. Leopold G. Koss
Performing Organization: Montefiore Hospital
City and State: Bronx, NY

Contract Number: N01-CB-84233
Starting Date: 9/30/78 Expiration Date: 9/29/81

Goal: To carry out an extensive study to test the feasibility of screening for endometrial cancers in asymptomatic women by means of uterine sampling.

Approach: Three thousand two hundred asymptomatic women over age 45 and up to age 70 years will be enrolled into the study. Sixteen hundred of the women will be in the age range 46 to 59 years and 1,600 will be in the age 60 and above. After history has been obtained and the examining procedure explained, each consenting examinee will receive a complete gynecologic examination, a vaginal pool smear, a cervical scrape smear, and an endocervical aspiration smear. Subsequently, the examinees will receive a Mimark or Isaacs (Curity) endometrial sampling randomly assigned by computer. The patient's acceptance of the procedure will be evaluated and recorded by the gynecologist upon completion of the examination. Results of the laboratory examination will be communicated by the contractor to the patient's primary physician and to the patient.

Progress: The enrollment of the examinees began on January 2, 1979. From that date until June 30, 1980, 1,784 primary eligible examinees received the clinical and cytologic examinations and the endometrial sampling described. There were 100 additional women who either refused to sign the informed consent or who were otherwise not eligible. Approximately 84% of the examinees were white and approximately 82% were 50 years of age or older. The endometrial procedure was successfully implemented in about 92% of the women with virtually no complications. Of the 1,784 examinees 146 were recalled at least once to clarify atypical or abnormal findings. Amongst the group of 1,784 examinees there were 8 endometrial carcinomas and 21 other endometrial abnormalities documented by histology (12 hyperplasias, 9 polyps). We also have failed in the identification of 1 confirmed endometrial cancer. As of January 1, 1980, a recall program of examinees seen 1 year before was begun. Between January 1 and June 30, 259 women returned for a repeat examination, giving a return rate of 37%. Some of these returnees may require additional follow-up. The total number of patients' visits during the reporting period was 2,189. It is of interest that 5 breast cancers, 1 ovarian cancer, 1 carcinoma *in situ* of the vulva, and 12 cervical intraepithelial neoplasias were also diagnosed in this asymptomatic population.

Project Officer: Dr. Bill Bunnag
Program: Diagnosis
FY 81 Funds: $193,440

CONTRACT RESEARCH SUMMARY

Title: Development of Electrophoretic Display Cell

Principal Investigator: Dr. Howard Sorkin
Performing Organization: North American Phillips Corp.
City and State: Briarcliff Manor, NY

Contract Number: N01-CB-04341
Starting Date: 9/30/80 Expiration Date: 3/29/82

Goal: To produce a large area electrophoretic display system for X-ray imaging which is suitable for use in clinical radiological diagnosis including tumor imaging.

Approach: The contractor will complete the production of an X-ray sensitive electrophoretic display system which was partially developed prior to the contract. The unit is basically a thin cell with a suspension of pigment particle in a dyed organic liquid held between electrode plates, one of which is transparent. Images produced by X-rays impinging on one of the electrodes, analogous to film sensitization by X-rays, will be visualized in the display cell by appropriate selective deposition of the pigment on the electrode surface. The system has a memory which is erasable by polarization changes in the electrodes. The specifications of the display cell proposed by the contractor are as follows: limiting resolution, 8 lp/mm; photopic contrast, 10:1; monochromatic contrast, 25:1; linear shades of grey, >500; saturation exposure, 0.5 mR; exposure for mid-grey level, 200 μR; image formation time, 100 ms; image retention time, >24 hr; image size, 10" x 10".

Progress: The development of improved PbO-binder layers has been separated into two distinct areas: mechanical methods of uniform layer deposition, and elucidation and optimization of the chemistry of the system. PbO-binder layers have been prepared by: rapid settling from dilute binder solutions; settling from viscous mixtures; direct application to a substrate using a blade to obtain correct layer thickness. The latter two methods give the most uniform layers as evidenced by radiographs of the dried, cured layers. To date, the most X-ray sensitive layers have been fabricated using alkydresin binders. These resins contain free organic acids which react with PbO to form lead salts. Efforts to determine whether these salts remain on the crystal surfaces and their effect on the X-ray performance of the binder layer are in progress. Two methods were developed for electrically evaluating PbO binder layers, viz., a dynamic (rotating) electrometer technique and a static capacitance technique. These techniques are being used to study the layers independently of the EPID cell. A method of permanently chemically bonding the stabilizer/charging agent to the pigment particles has been developed. Stable suspensions having the desired low pigment particle charge have been prepared using pigment modified by this method. Highly encouraging performance of X-ray imaging cells using these suspensions has been obtained. A method of removing impurities in commercially available dyes, by treatment with molecular sieves, has been developed. The purified dyes give suspensions with substantially lower conductivity and no electrohydrodynamic instability. Medical-quality X-ray equipment has been installed and approved for use by the contractor's radiation safety officer.

Project Officer: Dr. Bill Bunnag
Program: Diagnosis
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Innovative Techniques for Passage of Colonoscope

Principal Investigator: Dr. Max Epstein
Performing Organization: Northwestern University
City and State: Evanston, IL

Contract Number: NO1-CB-74114
Starting Date: 9/26/77 Expiration Date: 9/25/81

Goal: To develop safe and simple techniques and devices for early detection of small cancer lesions by means of endoscopic examination of the entire colon in order to improve life expectancy of postoperative patients and prevent or treat colonic cancer by endoscopic polypectomy.

Approach: Several devices will be investigated to enhance safety and ease of advancement of currently available colonoscope to the cecum. Prototype design, fabrication, and preliminary tests in simulated environment models during the first year will be followed by animal tests of promising designs during the second year. Also during the second year, the most promising devices will be fabricated in an appropriate form for clinical testing. During the third year the main efforts will be directed at clinical trials of one or more of the developed devices.

Progress: Three devices and several techniques have been developed. 1. The endoscopic extender, a miniature endoscope which can be introduced through the ancillary channel of the conventional endoscope, has been shown to be useful in animal tests and in patients. The results were published and further work awaits the design of a somewhat smaller device which can be more conveniently passed through most current colonoscopes. 2. The inflatable liner has been shown to be effective in tests in dogs and also in patients. Most recently, the device was modified to allow for the liner to be retracted, thereby facilitating its insertion and passage through bends and obstructions in the colon. A prototype liner utilizing water instead of air is currently being tested. 3. Several versions of an overtube were constructed which should greatly facilitate safe passage of the colonoscope, in particular, in the case of repeated insertion and withdrawal such as employed in multiple polypectomies. 4. A number of techniques to safely pass the presently available colonoscopes have been developed and will be described in a forthcoming report and will be submitted for publication.

In order to allow for the appropriate testing in patients, the research project has been extended for an additional (fourth) year at no cost.

Project Officer: Dr. Bill Bunnag
Program: Diagnosis
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Sera Collection from High Cancer Risk Populations

Principal Investigator: Dr. Henry Altschuler
Performing Organization: Philadelphia Geriatric Center
City and State: Philadelphia, PA

Contract Number: NO1-CB-33914
Starting Date: 6/25/73 Expiration Date: 11/24/80

Goal: To collect serial serum specimens from populations at high risk of contracting malignant disease for the purpose of developing and evaluating immunodiagnostic screening tests for human cancer.

Approach: Demographically stable populations at high risk of developing human malignancies in the colon, lung, breast, prostate, bladder, pancreas, etc. will be followed on an annual basis. This includes clinical evaluation and serum collection. The sera will be banked and kept on the patients so that information obtained from the stored sera can be correlated with development of any particular cancer.

Progress: Over the past 6 years and 10 months, a total of 4,211 serum specimens (divided into ten 1-ml aliquots) have been collected, processed, logged with assigned numbers on a chronological basis, frozen, and shipped frozen in dry ice to the Regional Serum Storage Center at the Mayo Clinic in Rochester, Minnesota. In addition, there is a patient card index, alphabetically organized by patient's name, and including age, sex, hospital MDI number, address, diagnosis, serum numbers (a label for each date of collection of blood placed on card), and date of collection of blood. There are additional cards which contain such information as the date of the last physical examination and information concerning such conditions as asthma, allergy, rheumatoid arthritis, desensitization therapy, immunization (influenza vaccine), and blood transfusions. Also maintained are a cancer index and a death index card file with significant findings at autopsy if performed. Data from these files have been collated on special computer adaptable forms supplied by NCI. An overall detailed clinical summary has been completed.

Project Officer: Dr. Bernice T. Radovich
Program: Diagnosis
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Tumor-Specific Antigens in Diagnosis and Management of Cancer Patients

Principal Investigator: Dr. T. M. Chu
Performing Organization: Roswell Park Memorial Institute
City and State: Buffalo, NY

Contract Number: NO1-CB-33858
Starting Date: 6/25/73 Expiration Date: 12/24/80

Goal: To study the relationship of CEA in the evaluation of recurrence and survival for cancer patients with curative surgery.

Approach: Examine the prognostic value of preoperative and follow-up CEA in relation to other preoperative variables; study the distribution profiles of CEA at surgery, during follow-up period, and at recurrence; implement a plan for patients whose risk of recurrence is greatest based upon preoperative and serial CEA; develop predictive models which integrate the CEA levels with other prognostic variables to determine the probability of recurrence in order to recommend adjuvant therapy.

Progress: An analysis of long-term follow-up CEA data and baseline data is under way on 74 patients with colorectal cancer and on 130 patients with lung cancer who underwent resections for cure. Of 74 colorectal cancer patients, 35 had recurrence of disease and 32 died. Preoperative CEA was found to be correlated with Dukes' classification, and had significant prognostic value between 9 and 18 months post surgery. Thereafter, Dukes' classification was a more significant predictor of disease recurrence. Matched-pair techniques revealed that CEA was often elevated in anticipation of recurrence, sometimes as early as one year prior to recurrence. The accuracy for using follow-up CEA events in predicting recurrence was restricted due to high false positive rates and low true positive rate. Further analysis is under way. Among patients experiencing recurrence, although forewarned by CEA elevations, no significant correlation was found between the time interval and risk of recurrence. The correlation of CEA evaluations alone with the time of recurrence was not strong enough to suggest a second-look surgery without other supporting evidence. In collaboration with NCI, a time-dependent Cox statistical model is being developed to re-investigate the relationship between follow-up CEA and disease recurrence. In patients with resectable lung carcinoma, CEA has more precise value in distinguishing, at an early date (sometimes at surgery), cured patients from those who would fail subsequent to surgical resection because of recurrent disease. Adjuvant therapies could thus be recommended for those patients with high risk for recurrence. In summary: (i) preoperative CEA is positively correlated with Dukes' classification; (ii) preoperative CEA adds significant information on Dukes' classification in the estimation of recurrence rates; (iii) postoperative CEA assays taken later in the clinical evaluation process carry the most prognostic information; (iv) CEA often rises in anticipation of recurrence; and (v) follow-up CEA events depending on multiple CEA observations have some accuracy in predicting recurrences but are of limited value in predicting the exact times of recurrence.

Project Officer: Dr. Bernice T. Radovich
Program: Diagnosis
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Application of Digital Image Processing Techniques to Cytology Automation

Principal Investigator:	Dr. James W. Bacus
Performing Organization:	Rush-Presbyterian-St. Luke's Medical Center
City and State:	Chicago, IL
Contract Number:	NO1-CB-74190
Starting Date:	9/30/77
Expiration Date:	9/29/81

Goal: Development of optimal algorithms for cell classification applicable to an automated digital image processing system.

Approach: The contractor shall conduct a comprehensive study to determine single cell vs. specimen classification accuracies for image processing algorithms and for cytotechnologists. This will determine how well the machine algorithms are performing. Five experimental tasks will be done: 1) sample acquisition, 2) cell acquisition, 3) observer recognition, 4) cell classification algorithms development, and 5) analysis and evaluation of results.

Progress: Patient selection and sample acquisition are essentially completed. Fabrication of the cell acquisition system is finished. Cells are being acquired routinely with this equipment. Programming of cell recognition algorithms continues with current emphasis on texture analysis and single cell classification. The observer recognition experiment is under way for single isolated cells out of context with background information and for single cells using the locally surrounding background information. Although the studies have not been completed--to date 23 observers have classified the same 1,650 cells, both with and without background information (from a targeted 10,000 cells, over 50 cases)--the preliminary results clearly indicate low classification accuracies for observers when they rely only on the information they can extract from single cells one-at-a-time. Since significantly abnormal (or positive) cells have a very low occurrence, these poor single cell performance characteristics of observers strongly suggest that traditional cervical cytology screening does not rely heavily on systematic location and classification of single cells one-at-a-time.

Project Officer: Dr. Bill Bunnag
Program: Diagnosis
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Isolation and Tissue Culture of Human Tumor Cells

Principal Investigator: Dr. Jørgen E. Fogh
Performing Organization: Sloan-Kettering Institute for Cancer Research
City and State: Rye, NY

Contract Number: NO1-CB-43854
Starting Date: 8/08/73 Expiration Date: 8/07/81

Goal: To develop further procedures for encouraging tumor cell growth in culture and to perform tests necessary to define standard cell lines from various tumors.

Approach: Human tumor cell lines are established in culture from surgical specimens and are collected from other investigators. They are characterized in this laboratory as to malignancy, cell type and special features as needed for individual investigations.

Progress: The contract supports a resource in the form of an extensive bank of human tumor lines grown in vitro. Cell lines are preserved after as few passages as possible, and are characterized in terms of morphology, nutritional requirements, growth in vitro, chromosomal characteristics and poliovirus susceptibility. They are monitored for microbial contamination. Analyses of polymorphic enzyme patterns enable the investigators to determine possible cross-contamination with other cell lines and to exclude such contamination when unique phenotype combinations are observed. The 426 cultured human tumor cell lines are available to other investigators. The bank now includes 69 melanomas, 31 carcinomas of the breast, 20 brain and nervous tissue tumors, 19 carcinomas of the bladder, 18 of the colon, 17 of the lung, and 10 of the kidney. Five hundred and sixty-four lines have been made available to other investigators in a 12-month period (1980), plus 238 for the period of 1/1/81 through 5/4/81, indicating a good utilization of the resource.

Project Officer: Dr. Bernice T. Radovich
Program: Diagnosis
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Ultrasonic Probes Inserted Through Endoscopes in Cancer Diagnosis

Principal Investigator: Mr. James L. Buxton
Performing Organization: SRI International
City and State: Menlo Park, CA

Contract Number: NO1-CB-74136
Starting Date: 9/30/77 Expiration Date: 1/31/81

Goal: To develop and clinically test an ultrasonic imaging system which will provide extremely high resolution images of the anatomy in the thorax and upper abdomen.

Approach: Currently available imaging systems have inadequate resolution to diagnose many diseases in organs in the middle of the torso. For instance, conventional imaging systems cannot diagnose pancreatic cancer until very advanced stages. The thrust of this project is to develop an ultrasonic imaging system with its transducer on the tip of an endoscope, so that internal organs can be imaged through the wall of the gastrointestinal tract. The resulting proximity to internal organs permits high resolution images and, in addition, eliminates the shadowing by bowel gas which plagues conventional ultrasonic systems.

Progress: By the end of the first year, the basic ultrasonic imaging system had been developed and demonstrated. The system is organized around a 64 element, 10 MHz, linear array which is 30 mm long. The 3 x 4 cm image is produced in a B-scan format at approximately 30 frames per second. Dynamic focusing on both transmit and receive provides submillimeter resolution in both dimensions throughout the field of view. Midway through the second year of the project, a prototype endoscopic imaging system was installed at the Mayo Clinic for tests with dogs. This first system included an endoscope with an outside diameter of 13 mm, side-looking optics and ultrasound, and a rigid tip length of 80 mm. This system demonstrated that intragastric imaging provides very high resolution imaging of the anatomy near the upper GI tract. Among the organs imaged were: heart, liver, both kidneys, gallbladder and biliary tree, spleen, and abdominal vasculature. Early in the third year of the project, an improved endoscope was completed. Changing the optics to look forward allowed the rigid tip length to be reduced to 40 mm. With this unit, preclinical trials were started in November 1979. In human control subjects, this system has imaged all of the organs that the first system imaged in dogs and, in addition, has demonstrated the entire pancreas. The system has successfully been used to diagnose a variety of diseases, including chronic pancreatitis, pancreatic abscess, pancreatic cancer, liver cancer, and stomach ulcers.

Project Officer: Dr. Bill Bunnag
Program: Diagnosis
FY 81 Funds: $50,000

CONTRACT RESEARCH SUMMARY

Title: Gelatin Encapsulated Microbubbles as Ultrasonic Contrast Agents

Principal Investigator: Dr. Barbara A. Carroll
Performing Organization: Leland Stanford Jr. University
City and State: Stanford, CA

Contract Number: NO1-CB-14337
Starting Date: 5/15/81 Expiration Date: 5/14/83

Goal: To determine the effectiveness of gas-filled microbubbles as contrast agents to be used in diagnostic ultrasound.

Approach: Appropriate sized gas-filled microbubbles will be produced and in vitro testing systems will be conducted. In vivo testing will be done in tumor-bearing animals to determine the ultrasound contrast characteristics of the microbubbles. Acute and chronic toxicity studies on promising microbubbles will also be done.

Progress: New Project.

Project Officer: Dr. Bill Bunnag
Program: Diagnosis
FY 81 Funds: $212,384

CONTRACT RESEARCH SUMMARY

Title: Alterations in Cellular and Humoral Anti-tumor Immune Reactivities

Principal Investigator: Dr. Isaac P. Witz
Performing Organization: Tel Aviv University
City and State: Tel Aviv, Israel

Contract Number: NO1-CB-74134
Starting Date: 9/30/77 Expiration Date: 7/29/81

Goal: Study alterations in the natural cellular and humoral reactivity patterns in mice at high risk of developing carcinogen-induced or endogenous virus-induced malignancies as well as serological reactivity of such mice toward antigens associated with the relevant tumors.

Approach: Characterize early alterations in naturally-occurring cellular and humoral anti-tumor immune reactivities in the following animal model systems: spontaneous tumors in C3HeB mice; mammary tumors induced by DMBA in BALB/c mice; and lung adenomas in urethan-treated BALB/c mice.

Progress: This contract is in its fourth year of work, studying alterations of serological and cellular reactivity patterns in mice at high risk of developing malignancies. The serologic pattern of normal mice has been established to serve as a basis for comparison of altered reactivity as carcinogen and viral-induced malignancies develop. The sequential serologic analysis of urethan-treated mice (those which developed lung adenomas and those which did not) throughout the carcinogenesis latency and the tumor-bearer periods has been completed. Sera from serial blood samples were analyzed by complement-dependent lysis (CdL) assays using 4 different tumor target cells. A statistical analysis has shown that the CdL of one of these targets mediated by serum of urethan-treated mice that developed tumors differed significantly from that of mice which did not develop tumors. This difference was first noted during the carcinogenesis latency period.

A time course study of NK activity in DMBA-fed mice was recently completed. Very early following DMBA administration the number of cells in the spleen of the treated animals was decreased to about 50% of normal values. The NK activity (calculated on a per cell basis) was also significantly decreased. These two effects caused a 4-6-fold decrease in the number of lytic units in the spleen of DMBA-treated animals as compared to normal controls. The number of splenocytes was spontaneously restored to normal values about 3 months following DMBA administration and before most animals developed tumors. On the other hand, the NK activity remained depressed throughout the entire carcinogenesis latency period. A further significant decrease in NK activity occurred in those animals which developed primary tumors. This further depression seemed to be secondary to tumor development and was mediated by suppressor cells.

Project Officer: Dr. Bernice T. Radovich
Program: Diagnosis
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Radioisotope Surface Markers and Detectors for Endoscopic Techniques

Principal Investigator: Dr. James M. Woolfenden
Performing Organization: University of Arizona Medical School
City and State: Tucson, AZ

Contract Number: NO1-CB-64012
Starting Date: 6/30/76 Expiration Date: 12/29/80

Goal: To establish a means for improving early detection of small cancer lesions on endoscopically approachable surfaces in order to improve the life expectancy of the patient.

Approach: A system will be developed for endoscopic detection of small cancer lesions in mucosal surfaces using tumor-seeking radioisotopic markers. A miniature radiation detector system suitably matched to emission characteristics of the isotopic markers will be developed. During the first year, work will center on development and testing of tumor-seeking markers. Initial detector design and construction will begin. During the second year, development of markers will continue, and candidate detector systems will be tested using a tumor phantom system. The period from the beginning of the third year to the termination of the contract will concentrate on patient studies to assess the sensitivity, specificity and accuracy of the tumor markers and detector system in localizing early cancer lesions.

Progress: Scintillation detectors made of thallium-activated sodium iodide and thallium-activated cesium iodide and a cadmium telluride semiconductor detector have been constructed. All have performed satisfactorily in tumor phantom studies, with better performance by the NaI(Tl) and CdTe detectors than the CsI(Tl). The NAI(Tl) detector is being used in clinical patient studies. The tumor-seeking marker is cobalt-57 bleomycin. External imaging is performed 24 hours after intravenous injection of 1 mCi Co-57 bleomycin; standard fiberoptic bronchoscopy is then done. The detector, coupled to an external photomultiplier tube by a flexible fiberoptic light guide, is passed through the bronchoscope biopsy channel, and counts are taken at sites throughout the bronchial tree. Data for 36 patient studies for which clinical follow-up information is available indicate detector sensitivity of 82%, specificity of 79%, and accuracy of 82% in locating tumors. Sensitivity of bronchoscopy including cytology and the detector combined was 91%; the two techniques appear to be complementary. Bronchoscopically invisible submucosal tumors and occult sources of malignant cytology can be found using the detector system in some patients.

Project Officer: Dr. Bernice T. Radovich
Program: Diagnosis
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: New Stains and Other Optical Markers for Cytopathologic Specimens in Suspension

Principal Investigator: Dr. Brian H. Mayall
Performing Organization: University of California
City and State: Livermore, CA

Contract Number: YO1-CB-40300
Starting Date: 6/01/74 Expiration Date: 7/31/81

Goal: To develop and evaluate stains that can be used in flow cytometry to differentiate normal from dysplastic and malignant gynecologic specimens.

Approach: The contractor shall: 1. Utilize flow cytometry to analyze 400 gynecologic samples stained in suspension with chromomycin A3. 2. Employ computer analysis to evaluate cellular DNA content and orthogonal light scatter signals. 3. Establish: a) error rates, system operating curves, and error cost curves with different cost structures, together with their 95% confidence ranges for assessment of the classification performance of the flow cytometric approach to automated gynecologic prescreening, b) performance criteria against which other systems may be judged, c) benchmark data in terms of which goals of the cytology automation program may be assessed.

Progress: We have established that flow cytometric measurement of cellular DNA content (as probed by chromomycin A3 fluorescence) and size (as probed by orthogonal light scatter) is able to detect premalignant and malignant cells when present in the sample. Treating specimens briefly with DNAse and centrifugal elutriation markedly reduces the incidence of false alarms due to clumps of normal cells, damaged cells, and non-human cell artifacts giving signals similar to those from abnormal cells. Sample diagnosis is based on the Atypia Index (AI) which is the ratio of Plain of Dysplasia signals (high fluorescence and moderate light scatter) to all epithelial cell signals. In a small pilot study, a specimen was classified as suspicious when its AI exceeded 0.5 percent. Comparison of machine classification with the cytomorphologic diagnosis indicated a false positive rate of 0.32 (12/33) and false negative rate of 0.09 (3/31).

The present study applies our protocol to greater numbers of specimens. Specimens from 85 healthy volunteers and from 80 women attending dysplasia clinic now have been collected and measured. This study already has demonstrated the feasibility of routinely measuring many samples. Analysis of the data will provide a statistically valid benchmark of the performance of flow cytometry in gynecologic prescreening.

Project Officer: Dr. Bill Bunnag
Program: Diagnosis
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Imaging Improvement and Evaluation in Detecting Early Pancreatic Cancer

Principal Investigator: Dr. A. R. Moossa
Performing Organization: University of Chicago Hospitals
City and State: Chicago, IL

Contract Number: NO1-CB-84232
Starting Date: 8/01/78 Expiration Date: 7/31/81

Goal: To compare, improve, and evaluate imaging methods and strategies applied to early detection and diagnosis of pancreatic cancer.

Approach: The imaging methods and strategies will be applied to the study of a selected population of patients in whom there is a high clinical probability of pancreatic cancer. The group will include patients with pathological conditions not related to the pancreas, patients with benign pancreatic disease, and patients with pancreatic cancer. The purpose of this study is to improve the ability of the diagnostic team to achieve rapid and certain identification of patients with early pancreatic cancer with the high probability group of patients. Patients must be over 35 years of age and in suitable physical condition to tolerate the necessary investigations and major abdominal surgery. They must have an estimated survival of at least three years. Both sexes will be included except for the exclusion of pregnant women. The study will be organized into five separate projects. All the various imaging methods to be investigated will be included in one of the four projects. The fifth project will be concerned with collection and evaluation of data gathered by the other four projects.

Progress: During the initial 30 months of the contract 113 patients with high clinical indications for probable pancreatic cancer have been entered into this study. Forty-four proved to have pancreatic cancer, 9 other cancers, 34 pancreatitis and 26 had a normal pancreas. The combination of ultrasonography, endoscopic retrograde cholangiopancreatography (ERCP), computed tomography and arteriography continues to show promising results. Preliminary radionuclide scans with ^{11}C-tryptophan are so much better than with ^{75}Se-selenomethionine that ^{11}C-tryptophan produced by the local cyclotron and scanned with a special positron camera are now being supplemented by scanning with the Phocon (longitudinal multiplane emission tomography which was originally performed following selenomethionine injection). Radionuclide scans are now performed both in fasting and in stimulated (after a meal; after injection of CCK-PZ or urocholine) state. Development of computer programs to produce a synthesized composite image by superimposing multiple images continues. The technical difficulties of ERCP scanning following retrograde injection of technetium microspheres and of computerized ultrasound have now been sorted out. All of these approaches will be continued during the next six months of this study.

Project Officer: Dr. Bill Bunnag
Program: Diagnosis
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Image Processing for Development of Automated Cell Recognition System

Principal Investigator: Dr. George L. Wied
Performing Organization: University of Chicago
City and State: Chicago, IL

Contract Number: NO1-CB-33873
Starting Date: 5/31/73 Expiration Date: 6/30/81

Goal: The total automation of clinical cytologic screening and diagnosis, focusing on definition of information requirements and criteria for high throughput, high resolution processing-based decision making.

Approach: The contractor evaluated information requirements for the characterization and recognition by means of digital image processing of normal, premalignant and malignant cells from specimens derived from the human female genital tract, and for a subsequent classification into a diagnostic category. The high resolution system is complete and ready for intensive field testing on real-world cell data.

Progress: Now fully automated (with the exceptions of automatically rotating the objective lens housing between medium and high resolution phases, and the automated insertion and removal of the specimen slide) the image processing and analytic system has been emendated by the addition of an improved scene segmentation technique using chromatic gradients to separate nuclei, cytoplasm and background, and cell classification performance has been significantly improved by the extraction of additional color and texture features, and Fourier shape descriptors calculated at high speed on the attached vector processor. Color images are now recorded on video tape, rather than being photographed, and zero-point and slide coordinate systems allow for quick relocation of cells on the original slide.

Excellent performance over a variety of diagnoses has been achieved using specimens preselected for good preparation and staining, ample cytologic material, and relative freedom from contaminants and artifacts. To evaluate "real world" performance, it will be necessary to use routine specimens of average quality. Classification algorithms need to be adjusted to account for the increased variety of artifacts, contaminants and staining differences likely to be encountered in this broadened sample space.

Project Officer: Dr. Bill Bunnag
Program: Diagnosis
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Statistical Center for Cooperative Lung Cancer Groups

Principal Investigator: Dr. C. Ralph Buncher
Performing Organization: University of Cincinnati Medical Center
City and State: Cincinnati, OH

Contract Number: NO1-CB-43868
Starting Date: 6/10/74 Expiration Date: 5/31/82

Goal: To collect and analyze information from the three clinical centers in the lung cancer screening program (which is directed toward the detection of early lung cancer in high-risk patients) to ascertain whether this screening program has reduced mortality and morbidity.

Approach: Procedures have been established with each of the centers and agreement has been reached concerning the common data base for this study. Data are routinely monitored by the Central Statistical Group (CSG), translated into a single computer data base in Cincinnati, and analyzed to provide the combined collaborative information as well as comparative information. Reports are made quarterly. The CSG will continue to search the data from this study for important and statistically significant findings.

Progress: The Cincinnati Central Statistical Group has established a common data base for this three clinical center study of screening to detect lung cancer at an early enough time to reduce mortality. Translation and reporting systems for each of the clinical centers have been created and analyses of collaborative results to date have been provided to the NCI and participating clinical centers. Intake of subjects has been completed so that adherence and compliance with the screening program is a current focus. Several thousand subjects have completed the screening program. Survival analysis efforts are being made by the CSG to obtain meaningful results with respect to mortality differences in the screening groups at as early a time as feasible. Regular Mortality Review Committee conferences are held to discuss the death certificate and best information causes of death for each man in the study who has died. Other central roles have been fulfilled by the CSG. In the first part of this contract, CSG was also responsible for a five-center study of computed tomography compared to radionuclide scanning and other methods of detection and diagnosis of brain tumors. Publications from that study have been issued. Similarly, CSG has worked with three centers concerning a collaborative study of pancreatic cancer diagnostic procedures; a number of reports from that study have been published.

Project Officer: Dr. Bill Bunnag
Program: Diagnosis
FY 81 Funds: $208,397

CONTRACT RESEARCH SUMMARY

Title: Cryopreservation of Human Monocytes for Use in Immunologic Studies

Principal Investigator: Dr. Roy S. Weiner
Performing Organization: University of Florida
City and State: Gainesville, FL

Contract Number: NO1-CB-74131
Starting Date: 9/30/77 Expiration Date: 12/31/80

Goal: To isolate human monocytes from peripheral blood and develop methods for their adequate cryopreservation.

Approach: Develop methods of collection and isolation of peripheral blood monocytes that would be applicable to normal subjects and to patients with cancer. Develop optimum techniques for cryopreservation and define the functional characteristics of cryopreserved cells.

Progress: To date, we have been successful in separating large numbers of monocytes from the peripheral blood using pheresis techniques. Up to 2×10^8 monocytes can be collected in 60 ml of buffy coat from peripheral blood using a standard Haemonetics Model 30 blood cell separator. Further, we have developed isolation techniques to obtain purified monocytes by elutriation centrifugation. We have modified techniques of Sanderson et al. so that up to 1.5×10^9 mononuclear cells can be loaded into the elutriation chamber and up to 3×10^8 monocytes are obtained in greater than 90% purity, representing 70% yield from peripheral blood. Additionally, we have separated a population of monocytes representing 15% of the total blood monocytes which are smaller than the large monocyte population. By fractionating the elutriation volume we were able to determine that these monocytes have a modal volume of 335 μ^3, whereas the large population of monocytes has a modal volume of 374 μ^3. We have also determined that while the native cytotoxicity attributed to monocytes is a function of the small population of monocytes, antibody cellular cytotoxicity is a function of both the small and large populations of monocytes. The antibody dependent cellular cytotoxicity is masked in the small population of monocytes unless that population is further purified to avoid steric hindrance. We have shown that cryopreservation by standard techniques is satisfactory for the maintenance of hexose monophosphate shunt activity, native cytotoxicity, chemotaxis, and antibody dependent cellular cytotoxicity.

Project Officer: Dr. Bernice T. Radovich
Program: Diagnosis
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Development of Contrast Agents for Use in Clinical Ultrasonic Diagnosis

Principal Investigator: Dr. Allan H. Gobuty
Performing Organization: University of Kansas Medical Center
City and State: Kansas City, KS

Contract Number: NO1-CB-84236
Starting Date: 6/26/78 Expiration Date: 6/30/82

Goal: To improve capability of ultrasound in the imaging of small tumors through the use of appropriate contrast agents.

Approach: Chemical compounds having the appropriate physical properties to influence ultrasonic signals will be identified and equipment will be assembled to test such compounds. Differential uptake of these compounds will be measured in animal tumor models. Animal toxicity studies will be made with promising compounds. Clinical trials will be conducted using the most promising agents after appropriate toxicity studies have been completed.

Progress: Compounds were selected and categorized ultrasonically by measuring the speed of sound, density and acoustic impedance as a function of concentration in aqueous solution. Two groups of substances in solution, amino acids and chelates, have shown promise because of their ability to measurably alter both the speed of sound and acoustic impedance, and because they possess useful pharmacologic properties. After completing preliminary lethality studies on these compounds to assess their acceptability for intravenous use in animals, one of them, Na_2Ca EDTA, was infused into the jugular vein on an anesthetized dog. Enhancement of echoes of canine renal cortex was noted. The results obtained indicate that the chelating agent produced observable changes in scattering and reflection properties of renal cortical tissue. Moreover, as a group the chelates appear to be less toxic than compounds discussed in our previous progress report.

Solid microspheres of collagen and gelatin, within the range of 2-10 μM diameter, have also been prepared. Measurements of the ultrasonic backscatter from these in suspension and from a standard RBC preparation were performed. When normalized to a standard particle size and concentration, the back-scatter from collagen was about 30 dB above RBC. Because of the expenses involved in preparation of collagen spheres, comparison was made with the ultrasonic properties of gelatin microspheres, both administered separately to anesthetized dogs. It was assumed that both these are taken up by RES cells. The canine experiments, using commercial diagnostic equipment (real-time linear array at 7 MHz), demonstrated enhanced backscatter from the liver shortly after intravenous infusion of each type of microsphere.

Project Officer: Dr. Bill Bunnag
Program: Diagnosis
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Purification of Human Tumor-associated Antigens

Principal Investigator: Dr. David Gold
Performing Organization: University of Kentucky Medical Center
City and State: Lexington, KY

Contract Number: NO1-CB-84259
Starting Date: 9/30/78 Expiration Date: 9/29/81

Goal: Purification, isolation, and identification of tumor-associated antigens.

Approach: Extract and purify colonic mucoprotein antigen (CMA) from normal colon and colonic adenocarcinomas; develop radioimmunoassay and immunohistochemical procedures for detection of CMA; investigate the potential of CMA as a tissue or tumor-specific marker.

Progress: This contract is concerned with the isolation of colonic mucoprotein antigen (CMA) and development of radioimmunoassay and immunohistochemical techniques for the detection of this organ specific antigen. During the first year emphasis was placed on purification of the antigen. A mucin fraction was obtained which by physicochemical criteria appeared to be relatively homogeneous. However, this material was found to be immunologically heterogeneous; two precipitin arcs were observed in immunodiffusion with homologous antiserum. In the second year we have studied the nature and relationship of these two components. Efforts to separate these two materials intact (including molecular sieve, ion exchange, adsorption, affinity, and electrophoretic techniques) proved fruitless; however, by protease digestion followed by molecular sieve chromatography we were able to separate the two components to apparent homogeneity, immunological as well as physicochemical. Analysis of these two materials has indicated that they are both mucins, one a sialomucin and the other a fucomucin. They were shown to be immunologically distinct, and the organ specific determinant was found only in the sialomucin. Immunohistochemical procedures have identified the organ specific determinant in 60% (total of 59 tumors examined) of colon carcinomas. Of particular note was the absence of the organ specific determinant in 14 gastric, 11 pancreatic, 9 endometrial and 5 bronchogenic tumors, many of which were mucin producers. Assays for monitoring levels of antigen in body fluids are being developed.

Project Officer: Dr. Bernice T. Radovich
Program: Diagnosis
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Immunohistochemical Studies of Tumor-associated Antigens

Principal Investigator: Dr. F. James Primus
Performing Organization: University of Kentucky Medical Center
City and State: Lexington, KY

Contract Number: NO1-CB-84257
Starting Date: 9/18/78 Expiration Date: 9/17/81

Goal: To isolate and characterize cancer-related markers in or on tumor cells by immunohistochemical techniques and describe their relationship to the discrimination of neoplastic cells from normal cells.

Approach: Studies will be performed using colon carcinoma antigen III (CCA-III), colon-specific antigen protein (CSAp), ßHCG, Regan isoenzyme, and major blood group antigens in an attempt to discriminate between malignant and non-malignant cells and to determine whether immunocytochemical methods can accurately detect metastatic spread in regional nodes.

Progress: Immunoenzyme staining for tumor antigens using glucose oxidase-anti-glucose oxidase (GAG) complexes gave similar localization and sensitivity as that obtained with PAP but without the inherent problems of endogenous enzyme activity associated with the latter. The GAG and PAP methods were combined to localize CEA and CSAp simultaneously. Excellent contrast and staining separation were shown between the enzymatic reaction products of the two systems. Immunostaining with the GAG method of 84 histologically negative nodes from 15 patients with CEA-positive primaries did not increase the incidence of tumor positive nodes. One of the latter nodes was positive for antigen localized within histiocytes. Immunostaining of a smaller number of histologically positive nodes showed complete agreement except in one case in which the primary tumor was of borderline positivity. CEA positive staining was demonstrated in 13 of 19 specimens of morphologically normal colonic mucosa reacted with the PAP method. Staining of normal colonic mucosa fixed in ethanol-acetic acid revealed a cytoplasmic localization of CEA in the columnar cell lining the mucosal surface and upper levels of the glandular crypts. CEA-specific localization was not observed in colonic goblet cells or in the small intestine. Comparative studies of blood group antigen localization with the immunoenzyme technique and SRCA test have demonstrated the superiority of the former method in detecting blood group antigens in intestinal, squamous, and transitional epithelium.

Project Officer: Dr. Bernice T. Radovich
Program: Diagnosis
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Screening Technique for Blood in Stool to Detect Early Cancer of Bowel

Principal Investigator: Dr. Victor A. Gilbertsen
Performing Organization: University of Minnesota Health Sciences Center
City and State: Minneapolis, MN

Contract Number: NO1-CB-53862
Starting Date: 6/30/75 Expiration Date: 6/29/81

Goal: To demonstrate a significant reduction in mortality due to colorectal cancer between the annually screened and the control group by employing the Hemoccult (R) form of the guaiac test for stool blood in combination with a diagnostic protocol for the source of bleeding.

Approach: Forty-five thousand participants between the ages of 50 and 80 years residing in the state of Minnesota are randomly allocated to three groups on the basis of age, sex and geographic location in the state. Slides are completed after the observance of a meat-free diet with suggested high fiber content. One of the groups completes the slides once per year, another every other year, and a third group which is unscreened serves as the control. Each slide set consists of 6 slides representing two from each of three consecutive stools. Participants submitting samples positive for blood receive a diagnostic examination (including a colonoscopy, UGI series, and proctoscopy) to determine the cause of bleeding. All diagnostic procedures are conducted at the University of Minnesota Medical Center. All data including pathology reports on biopsy material and surgical specimens are computerized for easy retrieval. Extensive follow-up procedures are designed to retain participation of all subjects throughout the five years of testing and an additional five years of follow-up. Extensive dietary and health history data are collected from each subject via questionnaire.

Progress: Significant progress to date includes completion of the first screen (both groups screened) and determination that 8% of the first screenees submitting at least 1 slide positive for occult blood and examined at the University of Minnesota (84%) were found to have at least one GI malignancy. The 16% examined elsewhere under a variety of protocols (most not including colonoscopy) have been accounted for and found to have a rate of 9% GI malignancies. The comparability of the two rates is being studied while the second and third screens are being completed. The diagnostic protocol for detection of the source of bleeding has been modified to exclude the single column B.E. x-ray subsequent to data indicating the superior uniformity of results using colonoscopic examination with air contrast B.E. x-ray (in those cases in which the cecum is not reached). Extensive follow-up procedures are followed to maximize continued participation and minimize attrition over the five-year screening and five-year follow-up periods.

Project Officer: Mr. Louis P. Greenberg
Program: Diagnosis
FY 81 Funds: $604,000

CONTRACT RESEARCH SUMMARY

Title: Antigens on Human Lymphoid Organs: Immunodiagnosis of Leukemias and Lymphomas

Principal Investigators: Dr. John H. Kersey, Dr. Tucker W. LeBien
Performing Organization: University of Minnesota
City and State: Minneapolis, MN

Contract Number: NO1-CB-84261
Starting Date: 9/30/78 Expiration Date: 9/29/81

Goal: To evaluate lymphoid differentiation antigens, particularly those on bone marrow and thymus cells, as potential immunodiagnostic markers for leukemia and lymphomas, and as markers for functional lymphoid cell populations.
Approach: To produce monoclonal antibodies against antigens present on the human pre-B acute lymphoblastic leukemia cell line NALM-6 MI and antigens present on human T lymphocytes. Use these monoclonal antibodies to a) examine the expression of the identified antigens on human leukemic cells, normal bone marrow and normal thymus, and b) characterize the identified antigens using immunochemical analyses.
Progress: Three new monoclonal antibodies have recently been produced and are undergoing extensive characterization.

Monoclonal Antibody BA-1: Produced by immunizing mice with the pre-B ALL cell line NALM-6-MI, BA-1 reacts with peripheral blood B cells, CLL, pre-B ALL, and most non-T, non-B ALL. BA-1 does not react with multiple myelomas, PWM-induced plasma cells, normal and malignant cells of T cell origin, monocytes, AML, AMML. The determinant recognized by BA-1 is not surface Ig, HLA-DR, Fc receptors, or C3 receptors. Immunochemical studies to date have shown that the cell surface antigen recognized by BA-1 is extremely sensitive to proteases. This characteristic has made it difficult to study BA-1 using radioimmune precipitation and SDS-PAGE, and we are still working on determining the molecular weight of the BA-1 antigen.

Monoclonal Antibody BA-2: Also produced by immunizing mice with the NALM-6-MI cell line, BA-2 recognizes a 24,000 dalton protein (p24) in SDS-PAGE. p24 is found on 70% of non-T, non-B ALL (including most pre-B), and 3-6% of normal bone marrow cells. Double fluorochrome studies have shown that some BA-2+ bone marrow cells are also TdT^+. p24 is also expressed on 50% of AML and CLL, but is present on 2% of peripheral blood mononuclear cells. This newly described hematopoietic progenitor/leukemia-associated antigen is clearly different from the previously described common acute lymphoblastic leukemia antigen (CALLA), the latter being a glycoprotein of 100,000 daltons.

Monoclonal Antibody TA-1: Produced by immunizing mice with the T ALL cell line HSB-2, TA-1 binds to all mature, peripheral T cells, 70% of thymocytes, and all peripheral blood monocytes. Studies with a $F(ab')_2$ of TA-1 show that this monoclonal antibody is reactive with AMML, but nonreactive with AML. TA-1 appears to react primarily with cells (malignant and nonmalignant) of T lymphocyte or monocyte lineage. Recent studies using radioimmune precipitation and SDS-PAGE have shown that TA-1 precipitates a bimolecular complex of 175,000/110,000 daltons.

Project Officer: Dr. Bernice T. Radovich
Program: Diagnosis
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Slit-Scan Technique as Cancer Prescreening Automated System in Cytology

Principal Investigator: Dr. Leon L. Wheeless, Jr.
Performing Organization: University of Rochester Medical Center
City and State: Rochester, NY

Contract Number: NO1-CB-33862
Starting Date: 3/19/73 Expiration Date: 3/18/82

Goal: Automation of clinical cytologic screening and diagnosis.

Approach: The contractor will evaluate the performance characteristics of the X-Y-Z Slit-Scan Flow System. A benchmark study of the X-Y-Z system will be performed to (1) determine system characteristics including rate and causes of remaining false alarms and (2) document true alarm rates for abnormal specimens. Correlation studies will continue and studies on second stage processing techniques will begin.

Progress: The X-Y-Z Slit-Scan Flow System has been fabricated and testing initiated. A spectrum of normal and abnormal clinical specimans is being used to evaluate system performance characteristics and establish a flow data base. Preliminary results are very encouraging. Three hundred and seven clinical specimens have been analyzed to date. The false positive rate on 185 normal specimens is 12.3 percent. The false negative rate for abnormal specimens representing squamous cell cancer and its precursors is 4.2 percent. Out of the 76 abnormal specimens, only three slight dysplasias were missed. For the full spectrum of abnormality, the false negative rate is 7.2 percent. All false negatives were specimens having less than one abnormal cell per 1,000 normal cells.

An alternate system concept has been tested to provide similar multidimensional slit-scan information from a less complex instrument. This new instrument has been shown feasible and would additionally provide a significant increase in system throughput. The static cell data base has been expanded and specimen preparation protocols continue to be evaluated and improved. Specifications for a cell sorter and second stage processor have been defined.

Project Officer: Dr. Bill Bunnag
Program: Diagnosis
FY 81 Funds: $359,716

CONTRACT RESEARCH SUMMARY

Title: Soluble Antigen-Antibody Complexes in the Circulation

Principal Investigator: Dr. Harold J. Wanebo
Performing Organization: University of Virginia Medical Center
City and State: Charlottesville, VA

Contract Number: CO1-CB-84262
Starting Date: 9/28/78 Expiration Date: 9/27/81

Goal: Determine the diagnostic significance of circulating antigen-antibody complexes in the sera of cancer patients, identify the source of the antigen, and develop a sensitive assay for its presence.

Approach: Patients in three tumor groups (breast, melanoma, colon) are being studied prospectively from presentation to determine the incidence and nature of immune complexes (IC) in serum and the changes in levels of IC that result from treatment. Immune complexes were identified by the presence of cryoglobulins and the Raji cell and C1q binding radioimmunoassays.

Progress: In 24 patients with primary breast cancer, IC were detected in 39% at presentation with the Raji cell RIA, the most sensitive assay. There was a significant rise in Raji binding complexes two months after surgery (71%) followed by a fall. Patients with benign breast lesions had similar incidence of IC (35%) although levels were lower. Metastatic cancer was associated with a similar incidence of IC (57%). Preliminary data suggested that estrogen receptor positive tumors were associated with a higher incidence of circulating IC.

In 18 primary melanoma patients, IC were detected at the onset in 25%. There was a similar increase, though less marked, in IC levels two months after surgery (46%). While there was a higher incidence of IC in patients with metastatic disease (57%), the absolute levels were not significantly higher than in those with primary disease.

In 22 patients with colorectal cancer, IC were detected preoperatively by at least one assay in 64%, by the Raji RIA 59%, by C1q binding assay in 18% and by cryoglobulins in 5.3%. The frequency of IC by Raji assay was greatest in patients with Stage III disease (Dukes' C cancer). There were correlations of IC with CEA depending on the method of IC determination. With respect to Raji cell RIA assay in 61 patients who had CEA tests above normal, Raji cell values (exceeding 25 μg equivalent AHG/ml) were detected in only 18.7% (4 of 22) of patients with CEA values $\geq$ 20 ng/ml compared to 41% (16 of 39 patients) with CEA values <20 ng/ml, $P = .02$. Examination of C1q results showed positive C1q binding assays (values >7.5% precipitation) in 11 of 137 serum samples. Of these, 6 occurred with CEA values of 5-19 ng/ml and 5 occurred with CEA > 100 ng/ml. Studies using sucrose density gradient ultracentrifugation and radioimmune diffusion showed that C1q was able to bind to CEA.

Project Officer: Dr. Bernice T. Radovich
Program: Diagnosis
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: A Serum Alkaline Phosphatase Variant (FHAP) in Cancer Patients

Principal Investigator: Dr. Frank C. Larson
Performing Organization: University of Wisconsin
City and State: Madison, WI

Contract Number: NO1-CB-74173
Starting Date: 9/15/77 Expiration Date: 12/14/80

Goal: To define the diagnostic and prognostic significance of an isoenzyme of alkaline phosphatase (FHAP) in serum of human cancer patients.

Approach: Serum of cancer patients often contains high level activity of a fast electrophoretically mobile, homoarginine sensitive alkaline phosphatase (FHAP), which is present only at low activity in normal persons and those with benign disease.

FHAP is ubiquitous among neoplastic diseases although some, e.g., carcinoma of the pancreas, lung and colon, are more likely associated than others, e.g., lymphomas. Initial studies were undertaken to examine the diagnostic implication of FHAP. The studies during the final year focused on cancer prognosis.

Progress: The positive relationship between serum FHAP activity and the presence of cancer has been confirmed. Based on the analysis of several thousand persons' serum, an upper limit of normal value of 2.1 U/L has been established. Most cancer patients have values above 2.1 U/L. Highest values are more observed in patients with extensive disease.

During the last year the research emphasis has been on comparing CEA and FHAP as tests of prognosis. Initially the approach was to compare FHAP values in patients whose prognosis was estimated to be good with those of patients whose prognosis was unfavorable. The mean (and median) value of patients who were judged to be cancer-free following surgical resection was substantially lower than the mean (and median) value of those who were believed or known to have cancer remaining. Of those with a favorable forecast, only 25% had values above normal (mean 1.86 U/L) while 62% of those with unfavorable forecast had above normal values (mean 9.27 U/L).

During the third year of the contract sequential FHAP and CEA values were compared in 250+ patients to determine if changes in FHAP and CEA were predictive of recurrence and if so how long before the clinical evidence of relapse appeared. The most common event was that neither marker became elevated and the cancer did not recur during the period of study. In those cases in which cancer did recur in most cases either FHAP or CEA or both were increased. The increase in the cancer marker often antedated clinical evidence of recurrence as much as several months. FHAP appeared to be a somewhat more sensitive marker than CEA but, more importantly, the two markers seem to vary independently.

Project Officer: Dr. Bernice T. Radovich
Program: Diagnosis
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Development of Large Area Solid State Image Receptors for X-Ray Imaging

Principal Investigator: Dr. Moshe Ein-Gal
Performing Organization: Xerox Corporation
City and State: Pasadena, CA

Contract Number: NO1-CB-74211
Starting Date: 9/30/77 Expiration Date: 6/30/81

Goal: To improve clinical diagnostic radiology and to provide for the diagnosis of early cancer by developing a computerized imaging system based on a large area solid state x-ray receptor superior in clinical usefulness to those currently available.

Approach: A large area solid state x-ray detector will be produced which will transform the x-ray flux into a digitally stored high quality image. The system to be developed, an x-ray selenium electronic linear scanner, will use the capability of a selenium alloy photoreceptor to create a latent image from absorbed x-rays. The latent image, a distribution of electric charge on the photoreceptor surface, will be detected by a microelectrometer scanning arrangement. Signals from the electrometer array will be coupled with the necessary control, display, and image storage memory components. Feasibility of the imaging system components will be developed in the first year. Further design, development, and optimization of the system will be completed during the second year. Clinical evaluation of the total imaging system will be conducted during the third year as well as further improvements and optimizations.

Progress: Initial assembly and feasibility testing of the detection components were accomplished during the first year as scheduled. The computer system, the dedicated image processing hardware and the x-ray facilities were installed during the second year of the contract. Since the beginning of the third year, the system has been prepared for hospital installation, a cassette scanner has been designed and a high resolution (1024^2) display unit has been fabricated. A team of radiologists for the clinical evaluation has been selected and the system was installed in the hospital June 1980. Imaging of live patients has begun. A cassette-oriented system has been developed and is undergoing physical testing. It is expected to start clinical evaluation May 1981.

Project Officer: Dr. Bill Bunnag
Program: Diagnosis
FY 81 Funds: $90,000

CONTRACT RESEARCH SUMMARY

Title: Characterization of HLA Antigen of Donor's Lymphocytes by Serotyping and Cellular Typing

Principal Investigator: Dr. Rene J. Duqesnoy
Performing Organization: Blood Center of Southeastern Wisconsin
City and State: Milwaukee, WI

Contract Number: NO1-CB-04337
Starting Date: 6/2/80 Expiration Date: 6/1/83

Goal: To analyze as carefully as possible the cell surface histocompatibility antigens of donors in order to analyze the relationship between these antigens and the ability of those donors' cells to mount appropriate immune responses.

Approach: Analysis of cell surface antigens is performed by two different detection systems: serology and cellular typing. The serologic analysis is performed using carefully screened alloantisera in assays of complement-dependent cytotoxicity. The cellular analysis is performed by analyzing the proliferative responses to homozygous typing cells (HTC typing) and by analyzing secondary restimulation of lymphocyte populations selectively immunized against alloantigens in primary response (PLT).

Progress: As of 6/1/81 approximately 120 donors had been typed by serologic techniques and 20 donors by homozygous typing cell (HTC) analysis. The analysis of results with normal donors has allowed a definitive description of the population association between the SB markers of a new HLA locus (defined in the Immunology Branch) and the previously known HLA markers. This association is surprisingly weak, indirectly suggesting that the SB gene may map quite some distance from the other HLA markers, and indicating that the SB markers will be useful new markers for population studies among normals and in disease. The results previously described in the summary of 12/2/80 regarding SB antigens in the disease Dermatitis Herpetiformis have been strengthened by studies of an additional 13 donors. Family studies are now in progress to determine whether the evidence for involvement of both the DR and SB phenotypes in prediction of the disease results from gene interaction or from linkage disequilibrium.

For further information see Annual Report #Z01-CB-05067 I, Z01-CB-05078 I, Z01-CB-05100 I, and Z01-CB-05101 I.

Significance to Cancer Research: Considerable evidence from animal models and from epidemiologic studies in humans suggests that host cellular immune responses are crucial in determining the outcome of neoplastic diseases. Cellular immune responses are under control by genes in the major histocompatibility complex (HLA in man). In order to therapeutically manipulate these cellular immune responses, we must first understand their normal operation and genetic control.

Project Officer: Dr. J. Stephen Shaw
Program: Tumor Immunology Program
Technical Review Group: Immunology Support Contract (Ad Hoc Review)
FY 81 Funds: $93,371

CONTRACT RESEARCH SUMMARY

Title: Maintain an Animal Holding Facility and Provide Attendant Research Services

Principal Investigator: Ms. Diana Hernandez
Performing Organization: Cor Bel Laboratories, Inc.
City and State: Rockville, MD

Contract Number: NO1-CB-04336
Starting Date: 11/1/79 Expiration Date: 10/31/82

Goal: Maintain colonies of inbred mice (10,000 animals), inbred rats (500 animals), and rabbits (20 animals) and carry out selected breeding protocols with these animals as specified by the project officer. These animals are to be maintained in support of intramural research programs in the Immunology Branch, NCI.

Approach: Colonies of mice, rats, and rabbits are to be housed and fed according to National Research Council standards. Technical manipulations and breeding are to be carried out as directed by the project officer.

Progress: Performance on this contract has been highly satisfactory. The animal colonies have been established and are being maintained according to National Research Council standards. Animal health has, in general, been excellent, and breeding protocols have been satisfactory. Recordkeeping and transferring of animals to and from the NIH Campus have all been satisfactory.

Significance to Cancer Research: This animal colony is necessary in support of intramural research programs in the Immunology Branch of NCI. Many of these programs are concerned with the immune response to cancer.

Project Officer: Dr. David H. Sachs
Program: Tumor Immunology Program
Technical Review Group: Immunology Support Contract (Ad Hoc Review)
FY 81 Funds: $295,500 ($68,500 estimated additional)

CONTRACT RESEARCH SUMMARY

Title: Study of Natural Cellular Immunity to Tumors in Mice and Rats

Principal Investigator: Mr. Brian Weatherly
Performing Organization: Cor Bel Laboratories, Inc.
City and State: Rockville, MD

Contract Number: NO1-CB-14346
Starting Date: 2/16/81 Expiration Date: 2/15/84

Goal: Study of natural cell-mediated cytotoxicity of mice and rats and/or their immune responses to tumor-associated antigens. Studies on in vivo resistance to tumors and correlation with in vitro cellular immune responses.

Approach: To study (1) the natural cell-mediated cytotoxicity against tumors of mice and rats, and (2) the factors influencing the levels of this reactivity and mechanism of cytotoxicity.

Progress: This project was just initiated by this contractor, after recompetition of the previous contract (NO1-CB-74093). The necessary training of personnel, transfer of animals, and setting up of techniques for in vivo experimentation have gone well and have been completed.

Mice which received leukemogenic doses of x-irradiation continue to be followed for the development of thymic lymphomas. Some mice have been inoculated with bone marrow from normal or irradiated mice to determine the effects on tumor development and on NK cell activity.

Breeding studies are being continued, to place the genes for low NK activity on other genetic backgrounds.

Project Officer: Dr. Ronald B. Herberman
Program: Tumor Immunology Program
Technical Review Group: Immunology Support Contract (Ad Hoc Review)
FY 81 Funds: $222,228

CONTRACT RESEARCH SUMMARY

Title: Administrative Support Services

Principal Investigator: Ms. Karen Meinzen
Performing Organization: CSR, Inc.
City and State: Washington, D.C.

Contract Number: 263-79-C-0021
Starting Date: 10/19/80 Expiration Date: 10/18/81

Goal: To support administrative staff in preparation of scientific meetings and the research components in accomplishing their administrative tasks.

Approach: Current staffing situation places excessive demands on the administrative staff in carrying out their responsibilities. This project is to support tasks in organizing overview meetings, scientific workshops, and in preparing pre- and post-conference materials. In addition, editorial support was available to researchers in satisfying specific demands and formats of scientific journals.

Progress: Ten conferences of standing committees and specially organized workshops were held. Excellent support was given to NIH conference on low level radiation, in preparation of post-conference materials. Four-hundred eighty publications of current research were edited to correspond to requirements of specific journals. Pre-conference activities were handled for a number of meetings. On-site support was provided to workshops and overviews. Seventy-five hundred reprints were handled through the storage/distribution facility. Invaluable assistance was provided in preparation of annual reports and program overview handbooks.

Project Officer: Ihor J. Masnyk, Ph.D.
Program: DCBD
Technical Review Group: Ad Hoc Committees
FY 81 Funds: $382,775

CONTRACT RESEARCH SUMMARY

Title: Computer Services

Principal Investigator:
Name/Address:
Performing
Organization:

Mr. Francis A. McDonough
Department of the Treasury
1435 G Street, N.W.
Washington, D.C. 20220

Contract Number: YO1-CB-90316
Starting Date: Nov. 15, 1979 Expiration Date: Sept. 30, 1981

Goal: To provide computer facility for mathematical computations related to biological systems modeling carried out in the Laboratory of Mathematical Biology and other groups in DCBD, NCI.

Approach: Facility is accessed through remote terminals.

Progress: This facility is used only in a backup capacity because our own VAX computer is taking over most of our computations.

Project Officer: Dr. Mones Berman
Program: Cancer Biology Support Site Visit Date: N/A
Technical Review Group: Ad Hoc
Relevance Review Group:
FY 81 Funds: $2,000.

CONTRACT RESEARCH SUMMARY

Title: A Screening System for Topical Chemotherapy of Mycosis Fungoides

Principal Investigator: Dr. Stanford Lamberg
Name/Address: Johns Hopkins University
Performing Organization: Baltimore, MD.

Contract Number: NO1-CB-63927
Starting Date: 6/30/76 Expiration Date: June 30,1981

Goal: To apply chemotherapeutic agents developed by DCT for topical treatment of mycosis fungoides, a cutaneous lymphoma.

Approach: Chemotherapeutic agents are obtained commercially and from the DCT, NCI, and these agents are being screened by clinical patch testing in patients with mycosis fungoides.

Progress: Investigative new drug applications have been obtained fromt the FDA and patch test screening of these agents has been performed at Hopkins and other affiliated institutions comprising the Mycosis Fungoides National Cooperative Group. Patch test of all available chemotherapeutic agents has recently been completed.

Significance for Cancer Research: (NCP Objective 6 Approach 2)

Project Officer: Dr. Gary L. Peck
Program: Biology Support
Technical Review Group: Ad Hoc Committee
FY 80 Funds: None

CONTRACT RESEARCH SUMMARY

Title: Melanoma Cell Vaccine in In Vitro Assays for Humoral and Cellular Cytotoxicity

Principal Investigator: Dr. Grace Cannon
Performing Organization: Litton Bionetics, Inc.
City and State: Kensington, MD

Contract Number: NO1-CB-53916
Starting Date: 5/10/81 Expiration Date: 10/9/81

Goal: To prepare cultured melanoma cells for immunotherapy vaccine and to harvest and store patient serum samples.

Approach: (1) Grow human melanoma cells free of contaminants, treat cells with neuraminidase, freeze under sterile conditions, and provide cells as needed for human immunotherapy. (2) Deliver patient blood samples to contract site, harvest serum samples, and store them at -70°C.

Progress: Since the previous contract research summary, 4 new batches of vaccine have been prepared from human melanoma cell lines UCLASM-6, UCLASM-12, and UCLASM-14. Vaccine preparations have met quality control tests. In addition, 58 serum samples were frozen and stored in 657 vials. No additional vaccine production is needed to finish the protocol. Litton Bionetics staff will continue to deliver vaccine to the NIH Clinical Center until the contract expiration date.

Significance to Cancer Research: The melanoma cell line vaccine will be used in a clinical immunotherapy trial.

Project Officer: Dr. John R. Wunderlich
Program: Tumor Immunology Program
Technical Review Group: Immunology Support Contract (Ad Hoc Review)
FY 81 Funds: $0

CONTRACT RESEARCH SUMMARY

Title: Studies of the Immune Response of Mice and Rats to Tumor Antigens

Principal Investigator: Dr. Grace Cannon
Performing Organization: Litton Bionetics, Inc.
City and State: Kensington, MD

Contract Number: NO1-CB-74093
Starting Date: 2/28/77 Expiration Date: 2/27/81

Goal: Study of natural cell-mediated cytotoxicity of mice and rats and of their immune responses to tumor-associated antigens. Studies on in vivo resistance to tumors and correlation with in vitro cellular immune responses.

Approach: To study (1) the natural cell-mediated cytotoxicity against tumors of mice and rats, and (2) the factors influencing the levels of this reactivity and mechanism of cytotoxicity.

Progress: The main emphasis has been on the role of natural killer (NK) cells in resistance against tumor growth in vivo. Isotopically labeled tumor cells were injected intravenously and their rate of clearance from the lungs and other organs assessed during the first 2-18 hrs. Clearance of the labeled tumor cells correlated well with known levels of NK activity. Mice given the carcinogen, urethane, were analyzed in regard to levels of in vivo cytotoxic activity during the latent period. Mice which were susceptible to carcinogenesis also showed transiently depressed NK activity and depressed in vivo clearance of labeled tumor cells, whereas strains of mice that were resistant to carcinogenesis did not show depressed reactivity. The carcinogenesis by urethane in susceptible mice could be diminished by administration of normal bone marrow cells at 7-14 days after the carcinogen, indicating that depression of host resistance may be a critical factor in tumor induction. The possible role of NK cells in radiation carcinogenesis also is being examined. Fractionated leukemogenic doses of x-irradiation were found to markedly inhibit NK activity of C57BL/6 mice and this depression could be reversed by spleen or bone marrow cells from normal syngeneic mice but not from beige mice. Preliminary results also indicate a higher tumor incidence in irradiated beige mice.

Extensive mouse breeding studies have been performed, to follow up on observations regarding the genetic basis for low NK activity in the A and SJL strains. It appears, from F_2 and backcross analyses, that one gene is responsible for the depressed reactivity and efforts are being made to place this gene on other genetic backgrounds, to facilitate studies on the role of NK cells in primary carcinogenesis.

Significance to Cancer Research: Understanding the relationship of in vitro assays to host resistance of tumors is an essential element in our ability to use these assays to monitor the clinical response to immunotherapy and to understand the role of various immune mechanisms in resistance to tumor growth. Recent findings with natural cell-mediated immunity may account for a significant portion of in vivo resistance to tumor growth, and may have important implications for immune surveillance.

Project Officer: Dr. Ronald B. Herberman
Program: Tumor Immunology Program
Technical Review Group: Immunology Support Contract (Ad Hoc Review)
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Maintenance and Development of Inbred and Congenic Resistant Mouse Strains

Principal Investigator: Ms. Martha McGowan
Performing Organization: Litton Bionetics, Inc.
City and State: Kensington, MD

Contract Number: NO1-CB-94325
Starting Date: 2/1/79 Expiration Date: 1/31/82

Goal: To maintain a colony of inbred pedigreed strains of mice which are needed to support ongoing NCI intramural research in transplantation immunology.

Approach: The contractor maintains a colony of approximately 40 special inbred and congenic resistant strains of mice by pedigreed brother-sister mating. Quality control testing is carried out at each generation by cytotoxicity typing of animals from each strain. Alloantisera are raised between mouse strains to assist in this quaity control typing, and sera and animals are shipped by the contractor to collaborating investigators at NIH and elsewhere.

Progress: The contractor has maintained all inbred and congenic resistant strains of mice in excellent condition. Breeding of each strain and of hybrid strains, recordkeeping, and quality control testing have all been highly satisfactory. A backcrossing program has been instituted for all congenic resistant strains in order to keep the backgrounds of these strains identical. This involves backcrossing of each congenic to the reference background line once every 6-10 generations. This program has also been very satisfactory to date. Two new recombinant H-2 haplotypes have been identified during the process of this backcrossing, and these have been bred to homozygosity and established as two new valuable inbred congenic strains.

Antisera for histocompatibility antigen typing have been prepared in a variety of combinations and have been found to be excellent reagents. A series of new strain-restricted typing sera have been produced in order to identify each strain in the colony and distinguish it from all other strains. Shipping of animals and sera to collaborating investigators at NIH and elsewhere has been very satisfactory. The animals shipped from these pedigreed colonies have generally been of excellent health and have provided breeding stock for the production of larger numbers of experimental animals in numerous laboratories.

Significance to Cancer Research: This animal facility is needed for the breeding and maintenance of these inbred congenic resistant strains of mice. These animals make possible research on individual histocompatibility antigens and, in particular, the role of the major histocompatibility complex in the transplantation of tissues and cells and in the immune response to cancer.

Project Officer: Dr. David H. Sachs
Program: Tumor Immunology Program
Technical Review Group: Immunology Support Contract (Ad Hoc Review)
FY 80 Funds: $256,763

CONTRACT RESEARCH SUMMARY

Title: Induction, Transplantation, and Preservation of Plasma Cell Tumors in Mice and the Maintenance of Special Strains

Principal Investigator: Martha J. McGowan
Performing Organization: Litton Bionetics, Inc.
City and State: Bethesda, MD

Contract Number: NO1-CB-94326
Starting Date: 3/1/79 Expiration Date: 1/31/82

Goal: Transplantation, preservation induction, and shipping of plasmacytomas, T- and B-cell lymphomas in mice. Breeding of rare strains of mice, hybrids, and wild mice.

Approach: To maintain a closed conventional colony of BALB/c, BALB/c sublines, and BALB/c congenic strains for use in plasmacytoma induction and for the maintenance of a bank of transplantable plasmacytomas and other lymphocytic tumors. The mice in this environment are suitable for long-term plasmacytoma induction studies and for the generation of congenic strains of the BALB/c background. New BALB/c congenic lines, carrying genes and chromosomal segments from the plasmacytomagenesis-resistant DBA/2 C57BL, C3H and CBA backgrounds are being bred for use in plasmacytoma induction studies to identify genes involved with the genetic susceptibility of plasmacytomagenesis. In addition, to maintain a screening bank of myeloma proteins for the detection of new antigen binding myeloma and to maintain a wild mouse colony.

Progress: The contractor has maintained a bank containing roughly 2000 frozen tumor lines. This bank is a source of standard plasmacytomas, lymphocytic tumors, mast cell tumors and histiocytomas that are shipped to other investigators. Approximately 400 shipments are made per year.

The contractor maintains 47 different inbred strains, 31 wild stocks, and is developing 48 congenic strains. These mice are used to produce animals for plasmacytomagenesis studies. Currently the contractor maintains approximately 19 studies involving 2868 mice. The wild mouse colony is now probably the largest in the U.S. It continues to provide an abundant source of new genotypes.

Significance to Cancer Research: Provides essential support for the study of plasmacytomagenesis (carcinogenesis) with the specific goal of determining the genetic basis of susceptibility to tumor induction by mineral oil. Supplies essential biological material for investigators studying the biology of neoplastic plasma cells, tumor immunology, the genetics of immunoglobulins, and immunoglobulin synthesis.

Project Officer: Dr. Michael Potter
Program: Tumor Immunology Program
Technical Review Group: Immunology Support Contract (Ad Hoc Review)
FY 81 Funds: $454,631

CONTRACT RESEARCH SUMMARY

Title: Radioimmunoassay of Immunoglobulin Molecules

Principal Investigator: Dr. James Harness
Performing Organization: Meloy Laboratories, Inc.
City and State: Springfield, Virginia

Contract Number: NO1-CB-63932
Starting Date: 3/14/81 Expiration Date: 3/13/82

Goal: To perform radioimmunoassays of immunoglobulin molecules IgM, IgA, IgG, IgD, and IgE in lymphocytes culture supernatants or in other biological fluids.

Approach: The contractor is to perform determinations of human IgG, IgA, IgM, IgD, and IgE, and mouse IgA and IgM by double antibody radioimmunoassay by procedures defined by the project officer and using reagents supplied by the project officer. This contract provides critically required research support for studies on the nature of immunodeficiencies that are associated with a high incidence of malignancy and on the cause of the immunodeficiency associated with malignancies of the B cell or plasma cell system. In addition, these studies are directed at defining retained immunological capabilities of T-cell leukemias.

Progress: The contract has established radioimmunoassays for IgG, IgA, IgM, and IgE of man and for IgA and IgM of the mouse. These assays have been used to quantitate the rate of immunoglobulin synthesis by pokeweed mitogen-stimulated, peripheral blood lymphocytes of man or of splenic lymphocytes of the mouse in in vitro cultures. Patients with a T-cell leukemia associated with the Sezary syndrome have been shown to have a malignant expansion of helper T cells whereas a patient with acute lymphocytic leukemia was shown to have a malignancy of the suppressor T cells. A subset of patients with common variable hypogammaglobulinemia has been shown to have excessive numbers of suppressor T cells that inhibit gamma globulin synthesis by B cells. Certain patients with post marrow transplant immunodeficiency have deficient B-cell function whereas others have excessive suppressor T-cell activity. Patients with multiple myeloma have hypogammglobulinemia due in part to excessive numbers of suppressor macrophages. These studies are defining the nature of disorders of the immune system that led to a high incidence of cancer. In addition, they provide information on the cause of immunodeficiency that arises secondary to certain forms of malignancy. Finally, these studies have provided insights into the retained functions of T-cell leukemias.

Significance to Cancer Research: These studies will help elucidate the abnormalities of the immune system associated with the development of cancer.

Project Officer: Thomas A. Waldmann, M.D.
Program: Cancer Biology Support
Technical Review Group: Ad Hoc Review Group
FY 81 Funds: $51,000

CONTRACT RESEARCH SUMMARY

Title: National Cancer Institute Immunodiagnostic Reference Center

Principal Investigator: Dr. James Harness
Performing Organization: Meloy Laboratories, Inc.
City and State: Springfield, VA

Contract Number: NO1-CB-63976
Starting Date: 7/11/80 Expiration Date: 7/10/81

Goal: To develop new assays for tumor-associated antigens, to use immunochemical techniques for the diagnosis of cancer, to evaluate humoral immune responsiveness of patients with cancer.

Approach: To use sensitive radioimmunoassays to quantitate human, monkey, and mouse alpha-fetoprotein and human chorionic gonadotropin in serum, to evaluate these assays both as diagnostic techniques for testicular, ovarian, and hepatocellular cancer, and as a means of monitoring the clinical response to therapy. The contractor performed tests of humoral competence of patients with cancer or immunodeficiency diseases. Solid phase radioimmunoassays and ELISA assays hve been established to measure antibodies produced by antigen stimulated human peripheral blood mononuclear cells.

Progress: In a wide-ranging study of 1,000 patients with nonseminomatous germ cell tumors of the testis or hepatocellular tumors, alpha-fetoprotein and HCG assays have been shown to be of great value as an adjunct to diagnosis, in staging, and as a tool to monitor the chemotherpay of these tumors. These assays are being performed in collaboration with eight groups in monitoring the treatment of patients with hepatocellular or testicular germ cell tumors other than seminoma. In all cases in which the marker was elevated, but where there was no clinical evidence of disease, a positive marker always reflected occult residual tumor. Humoral antibody assays have been established for ten antigens and these antibody assays are of critical importance in defining immune defects in patients with high incidence of neoplasia. The solid phase radioimmunoassays and ELISA assays for human antibodies produced by antigen stimulated human peripheral blood mononuclear cells have been used to identify the pathogenic defects that lead to primary immunodeficiency diseases associated with an increased incidence of malignancy. Disorders involving T helper cell deficiency, excessive suppressor T cell activity and B cells have been identified in these patients with primary immunodeficiency states.

Significance to Cancer Research: These studies are helping to establish the usefulness of these multiple immunodiagnostic tests in the diagnosis of cancer, or as a means of monitoring patients during and after therapy.

Project Officer: Dr. Thomas A. Waldmann

Program: Tumor Immunology Program
Technical Review Group: Immunology Support Contract (Ad Hoc Review)
FY 81 Funds: 0

CONTRACT RESEARCH SUMMARY

Title: Molecular Biologic Studies of Tumor Viruses

Principal Investigator: Dr. Richard S. Howk
Name/Address Meloy Laboratories
Performing Organization: Rockville, MD

Contract Number: NO1-CB-04342
Starting Date: 6-30-80 Expiration Date: 6-29-83

Goal: To provide support for studies of the structure and expression of tumor viruses.

Approach: Viral biochemical, serolgoic, and biological parameters are monitored in different systems to define the regulatory mechanisms of tumor virus expression and to relate the expression to tumor production.

Progress: Mouse cells transformed by Bovine papilloma virus or by viral DNA have been found to contain multiple unintegrated viral DNA copies in the absence of detectable integrated viral DNA. These results suggest that transformation in this system is induced and maintained by unintegrated viral DNA.

Efficient transformation by the p21 coding region of Harvey murine sarcoma virus (Ha-MuSV) DNA requires that the viral long terminal repeat (LTR) be ligated to the p21 coding region. Two independent p21 coding genes have been cloned from normal rat cell DNA; one gene is colinear with the viral p21 coding region, while the second gene contains intervening sequences. When the Ha-MuSV LTR is ligated to either gene, it can transform NIH 3T3 cellls, inducing high intracellular p21 levels.

The origin and formation of mink cytopathic focus-forming (MCF) murine leukemia virus (MuLV) has been studied. Endogenous MCF-like viral DNAs have been found in AKR and other mouse strains. The entire env of some non-pathogenic MCF viruses has apparently been derived from these sequences. In spontaneous murine thymic tumors, one or more of these MCF-like sequences have regularly recombined with a specific region of the 3' end of ecotropic env. Pathogenic MCF viruses also contain these ecotropic virus-derived recombinant sequences.

Significance for Cancer Research (NCP Objective 6 Approach 2)

Project Officer: Dr. Douglas R. Lowy
Assistant Project Officer: Dr. Ira H. Pastan
Program: Immunology Support
Technical Review Group: Ad Hoc Committee
FY 81 Funds: $240,000

CONTRACT RESEARCH SUMMARY

Title: Immune Status of Patients Undergoing Immunotherapy

Principal Investigator: Dr. Douglas M. Strong
Performing Organization: Naval Medical Research Institute
City and State: Bethesda, MD

Contract Number: YO1-DB-00319
Starting Date: 3/1/80 Expiration Date: 9/30/82

Goal: To study the immune responses of cancer patients to tumor-associated antigens and to provide support for the Laboratory of Immunodiagnosis, NCI, for its detailed studies of cell-mediated immunity to human cancer.

Approach: Immunological tests to evaluate and monitor the immunocompetence of patients and their response to tumor-associated antigens include lymphocyte stimulation by mitogens and autologous tumor antigens; rosette assays for enumeration of T cells; leukocyte migration inhibition assays against recall antigens and tumor-associated antigens; and studies of direct cytotoxicity and antibody-dependent cell-mediated cytotoxicity against various human tumor cell lines.

Progress: All of the assays for cell-mediated immunity, and the computer system for analyzing the data and correlating with clinical information, have been fully implemented and are being performed well. Alterations in cellular immune function are being analyzed in cancer patients who are receiving BCG or poly I:C, or who are being treated by passage of their plasma over Staphylococcus aureus-protein A columns. The changes related to these treatments are under current analysis.

During the past several months, a major emphasis has been placed on the monitoring of cancer patients receiving various doses of purified recombinant leukocyte interferon. Natural killer cell activity and several other immunologic parameters are being tested at frequent intervals.

Studies on proliferation of human T cells in the presence of T cell growth factor have been pursued and techniques were developed for consistent production of high levels of factor, by stimulation of normal lymphoid cells and certain B cell lines.

Significance to Cancer Research: These studies will provide important information regarding the usefulness of various assays of cell-mediated immunity for immunodiagnosis and for monitoring the clinical course of cancer patients. They should also provide the necessary data for determining the optional dose of various agents for biologic response modification.

Project Officer: Dr. Ronald B. Herberman
Program: Tumor Immunology Program
Technical Review Group: Immunology Support Contract (Ad Hoc Review)
FY 81 Funds: $285,181

CONTRACT RESEARCH SUMMARY

Title: A Study of Phylogenetic Aspects of Neoplasia

Principal Investigator: Dr. John C. Harshbarger
Name/Address The Smithsonian Institution
Performing Organization: Washington, D.C.

Contract Number: NO1-CB-33874
Starting Date: 7/1/73 Expiration Date: 6/30/82

Goal: To collect, examine, classify, and preserve neoplasms in cold-blooded vertebrate and invertebrate animals, and to study experimentally the development of tumors in lower animals.

Approach: The principal investigator directs the operation of a registry of tumors in lower animals. Specimens are acquired from personal field investigations or through submittal by other investigators. The specimens are examined grossly, histologically, and in some cases by electron microscopy. Diagnoses are established and the specimens are described. Field investigations and experimental inductions of tumors in lower animals are carried out. Publications of the findings are made. The Registry also serves in a consulting capacity to other agencies concerned with diseases in lower animals. A complete collection of the literature on neoplasms in ectothermic animals is maintained on computer tape and is available for retrieval. Data on specimen accessions is likewise stored in a computer system.

Progress: Specimen accessions during the past year numbered 152, bringing the total to 2371. The literature collection has been re-examined and irrelevant papers deteted, leaving 3755. Data from these have been stored on computer tape and are retrievable by author, species, organ, diagnosis, and other key words. About half of the new accessions were confirmed to be neoplasms, while the remainder were parasitic, infectious, toxic, traumatic, or developmental diseases. Neoplasms were mostly from teleost fishes, amphibians, reptiles, and molluscs. In the invertebrate phyla, lesions that appear to be neoplasms by morphological criteria were found only in molluscs and arthropods (insects alone represented) with the possible exception of one platyhelminth. About 50 types of neoplasms have been recognized to occur at relatively high prevalences in certain species in certain locations. Foreign contributions came from Canada, England, Australia, India, Germany, Netherlands, Egypt, Japan, and USSR.

Significance for Cancer Research: Field studies and anatomical studies indicate environmental carcinogens that may be of importance in human cancer epidemiology or may be useful in designing analytical experiments to determine mechanisms of tumorigenesis.

Project Officer: Clyde J. Dawe, M.D.
Program: Cancer Biology Support
FY 81 Funds: 180,200 Site Visit Date: No Site Visit

CONTRACT RESEARCH SUMMARY

Title: Preparation of Purified Wheat Proteins and Wheat Protein Fractions

Principal Investigator: Dr. Donald Kasarda
Performing Organization: U.S. Department of Agriculture
City and State: Berkeley, California

Contract Number: Y01-CB-60312
Starting Date: 10/1/80 Expiration Date: 9/30/81

Goal: To obtain chemically defined fraction of wheat gliadin for use in studies of gluten-sensitive enteropathy (coeliac sprue).

Approach: Wheat gluten will be chemically fractionated and subjected to cyanogen bromide cleavage. Homogeneous fragments of gliadin, as well as gliadin itself, will then be supplied.

Progress: The contractor has supplied alpha-gliadin according to the contract schedule. The alpha-gliadin has been used in in vitro studies of responses of lymphoid cells to defined gliadin preparations -- cells obtained from both patients and normals. Finally, alpha-gliadin has been used in a radiometric assay of anti-gliadin production by lympoid cells in vitro which will ultimately enable us to study the regulation of anti-gliadin responses in vitro.

Significance to Cancer Research: Gluten-sensitive enteropathy is a disease associated with a high incidence of malignancy. Elucidation of the pathogenesis of gluten-sensitive enteropathy will provide insight into the factors which lead to the onset of malignant disease.

Project Officer: Warren Strober, M.D.
Program: Cancer Biology Support
Technical Review Group: Breast Cancer Task Force Committee
FY 81 Funds: $18,600

CONTRACT RESEARCH SUMMARY

Title: Preparation and Analysis of Cell Surface Protein (CSP) Fractions

Principal Investigator: Dr. David Schlesinger
Performing Organization: University of Illinois
City and State: Chicago, IL

Contract Number: NO1-CB-74214
Starting Date: 9/30/80 Expiration Date: 9/29/81

Goal: To prepare and analyze the structure of cell surface protein.

Approach: The C-terminal fragment of CSP (fibronectin) is prepared by proteolytic cleavage, anion exchange chromatography, and high pressure liquid chromatography. Fragments of fibronectin are prepared by cleavage by trypsin, chymotrypsin, or thermolysin, followed by affinity chromatography on specific ligands such as collagen, actin, or heparin, followed by ion exchange or molecular sieve chromatography. The fragments are sequenced by sequenator or micro-sequencing protocols.

Progress: Sufficient amino acid sequence has been obtained from a C-terminal fragment of fibronectin to be able to compare with recombinant DNA information from another project. A routine protocol was established for rapid amino acid analysis and sequencing of small amounts of purified fragments, and primary sequence data has been obtained from four entirely new fibronectin fragments, each of which is unique in activity and sequence. Further primary structure analysis is needed to provide an understanding of CSP's multiple biological effects. However, the Investigator who initiated the project is now leaving the contractor, and sufficient expertise to continue the project is no longer available at the University of Illinois. This particular contract will therefore be terminated at the end of the contract year.

Significance to Cancer Research: CSP (fibronectin) is a major adhesive glycoprotein that is present in a variety of normal connective tissue and epithelial cell types and is absent from many types of cancer cells, especially metastatic cells. Knowledge of the structure of CSP will further the understanding of the cancer process.

Project Officer: Dr. Kenneth Yamada
Program: Cancer Biology Support
Technical Review Group: Ad Hoc Committee
FY 81 Funds: $25,942

CONTRACT RESEARCH SUMMARY

Title: Interaction of Exercise, Dietary Carbohydrate and Cancer Cachexia in Rats

Principal Investigator: Dr. Richard A. Ahrens
Performing Organization: University of Maryland
City and State: College Park, MD

Contract Number: NO1-CB-94327
Starting Date: 6/1/79 Expiration Date: 5/31/82

Goal: To investigate the separate and interactive effects of quantitatively imposed exercise and variation in dietary carbohydrate source on the systemic response of rats to growth of tumors.

Approach: The first phase of the project will consist of determining optimum ranges of exercise schedule and dietary carbohydrate needs. The second phase will consist of definitive studies of the effect of imposed exercise on the systemic effects of tumors.

Progress: The feasible limits for dietary and exercise regimens have been established. The effect of exercise on response to tumor has been studied for W256 carcinosarcoma. The interaction of exercise and dietary carbohydrate source in presence of W256 is now being studied.

Significance to Cancer Research: Information concerning the effects of imposed or encouraged exercise and of predominance of simple or complex carbohydrates in diet, or retardation of wasting and hypophagic effects of cancer will be of great importance to knowledge of origins and possible methods of combating cachetic decay in cancer.

Project Officer: Dr. Seoras D. Morrison
Program: Biology Support
Technical Review Group: Ad Hoc Committee
FY 81 Funds: $42,223

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